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TECHNICAL REPORT

Americium-241 Decorporation Model

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October 2014

HDTRA1-10-C-0025

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CONVERSION TABLE

Conversion factors for U.S. customary to metric (SI units of measurement)

| MULTIPLY TO GET | BY BY | TO GET DIVIDE |
|--|----------------------|--|
| angstrom | 1.000 000 x E-10 | meters (m) |
| atmosphere | 1.012 25 x E +2 | kilo pascal (kPa) |
| bar | 1.000 000 x E + 2 | kilo pascal (kPa) |
| barn | 1.000 x E – 28 | meter ² (m ²) |
| British thermal unit (thermochemical) | 1.054 350 x E + 3 | joule (J) |
| calorie (thermochemical) | 4.184 000 | joule (J) |
| cal (thermochemical)/cm ² | 4.184 000 x E-2 | mega joule/m ² (MJ/m ²) |
| curie | 3.7000 000 x E + 1 | giga becquerel (GBq)* |
| degree (angle) | 1.745 329 x E – 2 | radian (rad) |
| degree (Fahrenheit) | Tk = (t +459.69)/1.8 | degree kelvin (K) |
| electron volt | 1.602 19 x E – 19 | joule (J) |
| erg | 1.000 000 x E – 7 | joule (J) |
| erg/sec | 1.000 000 x E – 7 | watt (W) |
| foot | 3.048 000 x X-1 | meter (m) |
| foot-pound-force | 1.355 818 | joule (J) |
| gallon (U.S. liquid) | 3.785 412 x E – 3 | meter ³ (m ³) |
| inch | 2.540 000 x E -2 | meter (m) |
| jerk | 1.000 000 x E + 9 | joule (J) |
| joule/kilogram (J/kg) (absorbed dose) | 1.000 000 | Gray (Gy)** |
| kilotons | 4.183 | terajoules |
| kip (1000 lbf) | 4.448 222 x E + 3 | newton (N) |
| kip/inch ² (ksi) | 6.894 757 x E +3 | kilo pascal (kPa) |
| ktap | 1.000 000 x E +2 | newton-second/m ² (N-s/m ²) |
| micron | 1.000 000 x E – 6 | meter (m) |
| mil | 2.540 000 x E – 5 | meter (m) |
| mile (international) | 1.609 344 x E + 3 | meter (m) |
| ounce | 2.834 952 x E – 2 | kilogram (kg) |
| pound-force (lbf avoirdupois) | 4.448 222 | newton (N) |
| pound-force inch | 1.129 848 x E – 1 | newton-meter (N*m) |
| pound-force/inch | 1.751 268 x E + 2 | newton-meter (N/m) |
| pound-force/foot ² | 4.788 026 x E – 2 | kilo pascal (kPa) |
| pound-force/inch ² (psi) | 6.894 757 | kilo pascal (kPa) |
| pound-mass-foot ² (moment of inertia) | 4.214 011 x E – 2 | kilogram-meter ² (kg*m ²) |
| pound-mass/foot ³ | 1.601 846 x E + 1 | kilogram/m ³ (kg/m ³) |
| rad (radiation absorbed dose) | 1.000 000 x E – 2 | Gray (Gy) ** |
| rem (roentgen equivalent man) | | Sievert (Sv) *** |
| roentgen | 2.579 760 x E – 4 | coulomb/kilogram (C/kg) |
| shake | 1.000 000 x E – 8 | second (s) |
| Slug | 1.459 390 x E + 1 | kilogram (kg) |
| Torr (mm Hg, 0 degrees C) | 1 333 22 x E – 1 | kilo pascal (kPa) |

* The Becquerel (Bq) is the SI unit of radioactivity: 1 Bq = 1 event/s.

** The Gray (Gy) is the SI unit of absorbed radiation.

*** The Sievert (SV) is the SI unit of dose equivalent.

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Preface

The research and development work, described in this report, was conducted under subcontract for Gryphon Scientific, LLC (Gryphon) for the Joint Science and Technology Office (JSTO) of the Department of Defense (DoD) Chemical and Biological Defense (CBD) Program. JSTO is also the Chemical/Biological Technologies (CB) Directorate in the Research and Development (RD) Enterprise of the Defense Threat Reduction Agency (DTRA). Contract HDTRA1-10-C-0025 is titled *Medical Countermeasures for CBR Agents*.

This project was initiated by Ms. Nancy Nurthen, of the Information Systems Capability Development Division (J9-CB) and continued by Dr. Christopher Kiley. It was funded under DTRA Contract Number HDTRA1-10-C-0025 to Gryphon Scientific, LLC, with subcontractor Applied Research Associates, Inc. (ARA). The target application for the product of this contract is under the auspices of the Joint Project Manager for Information Systems (JPM IS) of the Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD).

Section 1.

Executive Summary

A model for the treatment of americium-241 (Am-241) internal contamination by trisodium calcium and trisodium zinc diethylenetriamine pentaacetate (DTPA) was developed to evaluate the efficacy of various treatment regimens. The baseline uptake and decorporation model was developed by implementing existing models for inhalation exposure, uptake/respiratory clearance, and physiologically-based biokinetic distribution for americium. A treatment model for DTPA decorporation of americium was developed, along with a radiation dosimetry model for calculating doses; these models were integrated with the baseline model. The composite Am-241 decorporation model presented in this work estimates americium deposition, absorption, distribution, retention, excretion, and response to DTPA treatment in adult healthy males after an inhalation exposure. The model further estimates the acute red bone marrow and lung doses, as well as the whole body effective dose as a function of time. The results of the model compare favorably with human and animal data and provide estimates within the uncertainty limits of alternative models developed by the International Commission on Radiological Protection (ICRP) and the National Council on Radiation Protection and Measurements (NCRP). Outputs from the model include the distribution of americium deposited in the respiratory tract, the amount of Am in different tissue compartments over time with and without treatment, Am-241 excretion rates, and radiation doses to critical organs. Calculations from the model may be used to analyze consequences of exposure to Am-241 and the effect of treatment, based on different initiation and duration times. The model may facilitate interpretation of Am-241 bioassay data and aid in treatment planning. The Am-241 decorporation model is a valuable and versatile tool for assessing the effect of exposure to Am-241 and subsequent DTPA treatment.

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Section 2.

Introduction and Purpose

Accurate modeling of medical countermeasure efficacy against chemical, biological and radiological agents (CBR agents) is essential to understanding the vulnerability of our war fighters on the modern battlefield. In helping to calculate the benefit of countermeasures, modeling can inform data-driven purchasing decisions and logistical tradeoffs. In this study, Gryphon Scientific and Applied Research Associates, Inc. (ARA) have developed models to predict the efficacy of medical countermeasures in preventing casualties and reducing the severity and duration of illness caused by CBR agents.

This volume (prepared by ARA) is one of three, describing the medical countermeasure models constructed for this project. This volume focuses exclusively on the modeling approach, parameters, and calculations used for the medical countermeasure model (MCM) for americium-241 (Am-241) internalized contamination. The composite model includes the appropriate parameters necessary for calculating the impact of trisodium calcium and trisodium zinc diethylenetriaminepentaacetate (Ca-DTPA and Zn-DTPA) countermeasure treatment of Am-241 internalized contamination. Other volumes describe the *Francisella tularensis* model and the sulfur mustard model.

This paper presents an inhalation exposure model for calculating the deposition fraction of Am-241 in different regions of the respiratory tract from a given air concentration. The paper also presents an uptake/clearance model for Am-241, which describes the rate of transfer of Am from the respiratory tract to the systemic circulation or the gastrointestinal tract. Subsequently, a biokinetic model that describes the systemic distribution of Am-241 within the body, a DTPA model for binding and removal of Am-241 in the systemic circulation, and a radiation dose model for calculating the absorbed radiation dose in the whole body and to two critical organs, the red bone marrow and the lungs, is presented. Each model approach is described and justified along with the assumptions and key parameters that are implemented in each model. The composite model connects each set of calculations and is collectively used to calculate the acute and committed radiation doses, which can be related to potential adverse health effects. The radiation dose with and without DTPA treatment can be calculated and compared to determine efficacy of treatment. Different treatment initiation times and treatment duration times can be evaluated to determine the impact of different treatment scenarios on radiation dose.

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Section 3.

Background and Methodology

3.1 Importance of Americium-241

Americium (Am) is a man-made element with no stable isotopes. The most widely used isotope of americium is Am-241, which decays to neptunium-237 by alpha emission, followed by a low-energy gamma emission. Am-241 has a half-life of 432.2 years. Because of its long half-life and high specific activity, Am-241 is well-suited for use in radioactive sources, including alpha and photon sources, as well as neutron sources when combined with beryllium. Radioactive sources are used for a number of industrial applications that range from oil well logging devices, used to obtain geological information about the holes that are drilled, to use in home smoke detectors. The relative chemical stability of americium oxide (AmO₂) powder, encased in stainless steel, makes it the most commonly implemented form of Am-241 found in industrial sources (ORNL 1962, NRC 2008). A large number of Am-241 sources exist as unwanted sources that have no direct disposal route (NRC 2008). The National Nuclear Security Administration's Offsite Source Recovery Project has recovered over 10,000 (>13,000 Curies, Ci) abandoned or unwanted Am-241 sources. More than 6,000 Ci of Am-241 sources are in active use with over 1,000 sources reported as in excess or unwanted (NRC 2008). Such sources represent a potential security threat if acquired and used in a radiological dispersal device (RDD).

3.2 Americium-241 Decorporation

The pharmaceutical countermeasure, diethylenetriaminepentaacetate (DTPA), is the only FDA-approved decorporation agent for the actinides americium (Am), plutonium (Pu), and curium (Cm). DTPA, shown in its acid form, in Figure 1, is a chelating agent with amino- and carboxylic acid groups that can coordinate and bind actinides with relative high affinity and enable enhanced renal excretion of these radionuclides. DTPA can be administered by intravenous drip or direct injection into a vein as the calcium (Ca) or zinc (Zn) salt in a 5 mL hyperosmolar solution. The optimal dosing regimen for an adult is 1 gram (g) of Ca-DTPA on the initial day of treatment, followed by 1 g Zn-DTPA per day for subsequent treatments, until the radionuclide burden is adequately reduced (FDA 2004). For pregnant or lactating women, treatment should begin and continue only with Zn-DTPA (NCRP 2008).

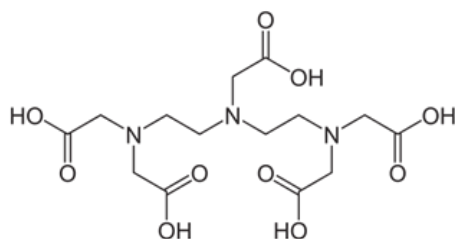


Figure 1. Diethylene Triamine Pentaacetic Acid, DTPA

Human and animal data indicate that DTPA effectively increases the rate of elimination of Am-241, which then in turn reduces the radiation dose absorbed by the body. While DTPA reduces the absorbed radiation dose, it does not treat the effects of radiation dose such as hematopoietic cell damage and loss. The benefit of DTPA treatment depends on the total Am-241 absorbed into the body and the time to DTPA administration. The actinide elements can be incorporated into bone and result in long term retention of the nuclides. Early administration of DTPA can minimize the radionuclide deposition in the bone and afford greater reduction of radiation dose and countermeasure efficacy.

3.3 Composite Model Approach

This paper presents a composite model for determining the efficacy of DTPA treatment of internal contamination if Am-241 and includes a description of the parameters used in each of the sub-model components. The sub-model components include:

- An inhalation exposure model for calculating the deposited pulmonary and ingested fractions of americium-241 from a given air exposure concentration.
- An uptake model for absorption from the pulmonary region and the GI tract.
- A biokinetic model for calculating the distribution of americium within the body.
- A radiation dosimetry model for calculating the absorbed radiation dose to critical organs for estimating acute effects and the projected whole-body dose over 50 years for long-term effects.
- A biokinetic model of DTPA for binding and removal of americium in the systemic circulation.

Each model approach is discussed and justified along with the key parameters for each model set. Collectively, these models can be used to calculate the acute radiation dose to critical target organs for determining acute effects, as well as the long-term committed radiation dose. The difference in the radiation dose resulting from different DTPA treatment regimens, including varying the start time and the duration of administration can also be calculated and compared. The composite modeling approach is outlined in Figure 2. The parameters necessary for calculating the effect of DTPA countermeasure treatment of americium-241 are further outlined for each model component in the next section.

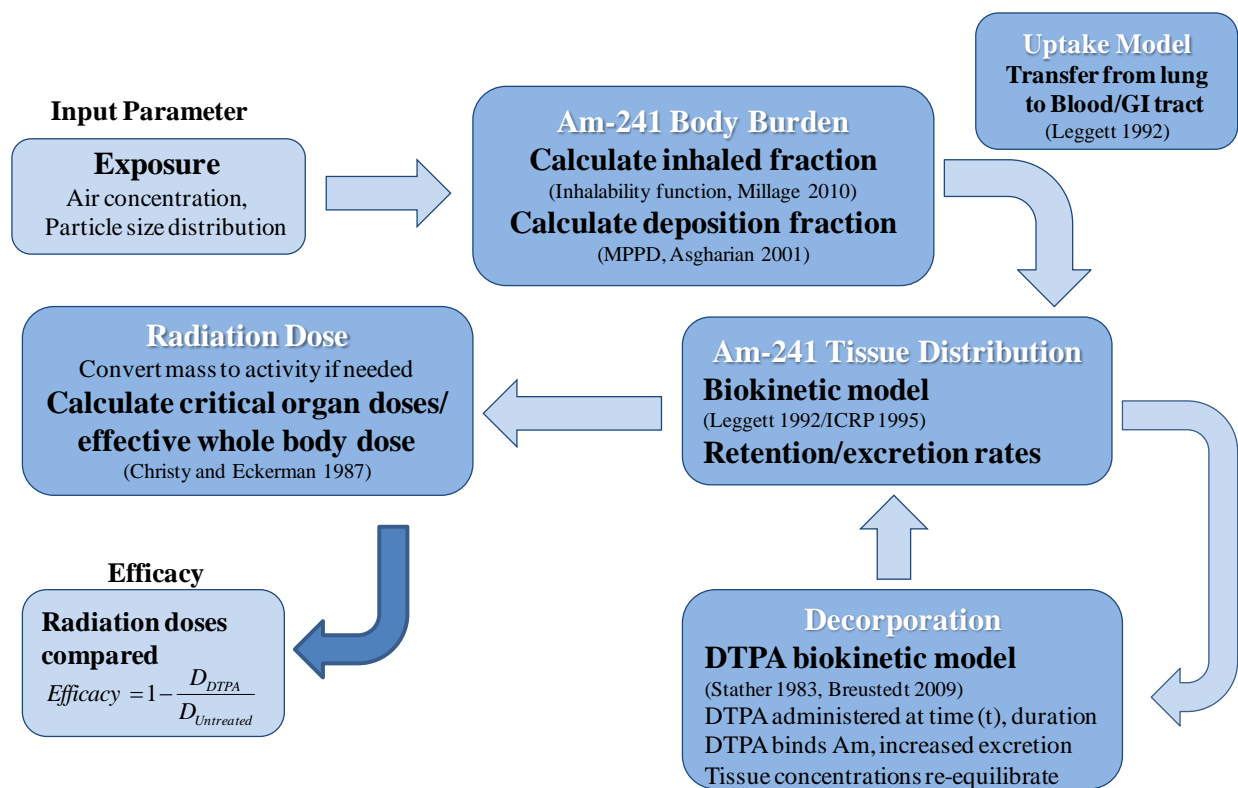


Figure 2. Composite Am-241 Decorporation Model Components

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Section 4.

Americium-241 Decorporation Model

4.1 General Assumptions

4.1.1. Exposure

The current modeling effort addresses the battlefield scenario in which an RDD is deemed the most likely threat scenario. Persons involved in an RDD event may be exposed to a significant amount of radioactive fallout, which would potentially result in skin contamination and inhalation of radioactive nuclides. Since the focus of the current work is the development of models for assessing medical countermeasures for internalized radionuclides, the primary route of exposure for internalization of radionuclides is through inhalation. Some of the inhalation exposure will result in the eventual transfer of material to the gastrointestinal tract and is addressed through the inhalation model. Ingestion is not currently considered a stand-alone route of exposure for the battlefield scenario.

The amount of Am-241 internalized as a result of dermal absorption from skin contamination is assumed to be negligible. Only in cases of heavy contamination of a soluble radionuclide would absorption through the skin result in any significant internalized contamination (NCRP 2009a). Americium oxide (AmO_2), the chemical form used in this modeling effort, is not readily soluble. Personnel clothing provides significant protection from skin contamination, and external decontamination can be readily performed.

External exposure to radionuclides from an RDD-type scenario can potentially result in a significant contribution to radiation dose but it depends on the specific radionuclides involved. For the specific case of Am-241, the primary contribution to radiation dose is from the alpha emission with a minor contribution from the low-energy photon. The alpha particle cannot penetrate past the epidermis and therefore does not pose a significant external hazard. Furthermore, any countermeasure treatment for the external dose contribution would be targeted toward acute radiation syndrome rather than decorporation. As stated previously, this particular modeling effort addresses internal contamination and decorporation treatment. Although modeling the impact of treatment on the dose contributed from external radionuclide sources would be valuable in number of scenarios, it is beyond the scope of the current work.

4.1.2. Physical and Chemical Form

As will be demonstrated in the results section, the physical and chemical form of the americium particles are critical to accurately estimating the americium distribution and resultant radiation dose from an inhalation exposure. Mono-dispersed particle sizes, ranging from 1 – 100 μm represent the majority of potential exposure scenarios and form the limits of the current model. Particles in this size range will generally deposit in different areas of the respiratory tract; larger particles will preferentially deposit in the upper respiratory tract and extrathoracic region, while small particles can reach the lower respiratory tract and pulmonary regions. These deposition parameters are estimated using the respiratory model described below. This approach allows the user to examine the influence of particle size on deposition, Am distribution, and dose.

The most common chemical form of Am-241 used in industry and found in nuclear waste is AmO₂, which affords limited solubility (NRC 2008). Americium is readily oxidized (ORNL 1962) and AmO₂ is commonly used in radioactive sources. Therefore, this chemical form is the form most likely to be encountered in an RDD scenario and has been chosen for the current modeling effort.

4.1.3. Inhalation Exposure

As described above, inhalation exposure was considered the primary route for americium intake for the modeling scenario chosen for this work. In the case of AmO₂, which has moderate solubility, the precise deposition in the respiratory tract will greatly impact the rate and amount of Am-241 reaching the systemic circulation. The inhalation model described below can estimate the regional deposition location of americium in the respiratory tract if key variables, such as particle size and wind speed are known. Reasonable default parameters are provided when specific scenario information is not available. When comparing our results with other established models, dose coefficients, or cases studies, parameters are chosen that most closely resemble the specific comparison presented.

4.1.4. Ingestion Exposure

Given the RDD scenario, ingestion is not considered a stand-alone route of exposure. A portion of the Am deposited in the respiratory tract will be eventually cleared by transfer to the GI tract. AmO₂ is not readily absorbed by the GI tract (0.02-0.05%, Leggett 1992, ICRP 1993), but the fraction of Am reaching the systemic circulation from the GI tract is accounted for.

4.2 Inhalation Exposure Model

The americium body-burden results from an exposure to a given air concentration of Am-241. The body-burden is calculated by considering the inhaled fraction of that exposure and the amount of the inhaled fraction that is deposited into the different respiratory regions. Both of these parameters depend on particle size and both are important to providing an accurate representation of the amount of americium retained from the exposure. An overview of the inhalation model used to calculate the americium body-burden is provided in Figure 1 and the details of the model are described in the following subsections. However, for a complete description of these previously established models, see the associated references.

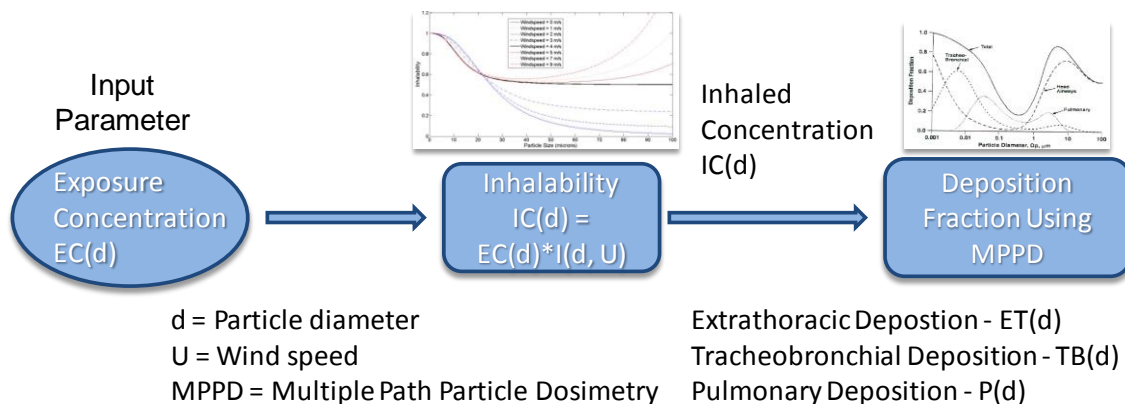


Figure 3. Inhalation Model

4.2.1. Inhaled Fraction

The inhaled fraction, $I(d_{ae})$, is determined by the particle size and air concentration:

$I(d_{ae}) = C_{inspired}(d_{ae}) / C_{ambient}(d_{ae})$ where $I(d_{ae})$ is the inhaled fraction by aerodynamic particle size (d_{ae}) and C is the particle concentration.

Inhalability is a measure of the air concentration of material that is inhaled, relative to the concentration in the ambient air; inhalability only refers to the intake process and does not account for deposition. A recent review examined the data from inhalability measurements and current mathematical models of inhalability (Millage 2010). Based on this review, a mathematical model was developed, providing the best description of the data across a variety of conditions, while minimizing mathematical inconsistencies, which we implemented in our work (see Millage 2010 for a complete description). The inhalability model is a function of both particle size (d_{ae}) and ambient wind speed (U) (wind speed can play a significant role in how much particulate material can be inhaled). The equation also takes into account the fraction of inhalation that is nasal (f_N) or oral (f_O). The nasal versus oral fraction can depend on breathing rate; most people breathe 100% through their nose until their breathing rate reaches 35 liters per minute and then they begin breathing through their mouth, as well.

Three equations are used to create a piecewise continuous model of inhalability to include the effects of wind speed, particle size and breathing function; each equation describes different wind speed regimes. The first equation is for still air, i.e. wind speed is zero.

$$I_{Still}(d_{ae}) = f_N \left[1 - \left(\frac{1}{1 + 6.809 \cdot 10^3 d_{ae}^{-2.736}} \right) \right] + f_O \left[\frac{1 + 0.44}{1 + 0.44 \exp(0.0195 d_{ae})} \right]$$

The next equation is for winds speeds (U) greater than zero, but less than or equal to 4 meters per second (m/s).

$$I_{0 < U \leq 4 \text{ m/s}} = (1 - J) \left\{ f_N \left[1 - (1 + \exp(8.826 - 2.736 \ln d_{ae}))^{-1} \right] + f_o \left[\frac{1.44}{1 + 0.44 \exp(0.0195 d_{ae})} \right] \right\} \\ + J \left\{ 1 - 0.5 \left[1 - (7.6 \times 10^{-4} (d_{ae})^{2.8} + 1)^{-1} \right] + 1 \times 10^{-5} U^{2.75} \exp(0.055 d_{ae}) \right\}$$

$$\text{where: } J = \frac{U^{2.75}}{4^{2.75}}$$

The final equation is for wind speeds greater than 4 m/s and less 10 m/s.

$$I_{4 < U \leq 10 \text{ m/s}}(d_{ae}) = 1 - 0.5 \left[1 - \frac{1}{7.6 \times 10^{-4} (d_{ae})^{2.8} + 1} \right] + 10^{-5} U^{2.75} \exp(0.055 \cdot d_{ae})$$

Note that these equations are not applicable for particle sizes greater than 100 microns in aerodynamic diameter. Often particles larger than a few microns are ignored because generally thought is that they will not be inhaled; however, larger particles can be inhaled and while they may not reach the pulmonary region, they can deposit in the extrathoracic region and be absorbed into the bloodstream. As an example, based on the equation shown above, in a moderate wind environment of 4 meters per second approximately 60% of 22 micron particles will be inhaled.

4.2.2. Inhaled Concentration

The inhaled concentration, $IC(d)$, is the ambient or presented concentration of radioactive particulate in the air multiplied by the inhalability function:

$$IC(d) = EC(d) \cdot I(d, U),$$

where EC is the exposure concentration by particle size diameter, d , and I is the inhalability function in terms of particle size diameter, and wind speed, U . The resultant inhaled value is the radioactive material concentration that actually enters the nasal or oral cavities; it does not take into account the fraction of the material that is deposited in the respiratory tract.

4.2.3. Wind Speed

If wind speed conditions are known, the model will allow a user-specified value; otherwise a default ambient air speed value of 4 m/s will be used.

4.2.4. Deposition Fraction

The deposition fraction is the fraction of inhaled radioactive material that is deposited in specific regions of the respiratory tract. We used the Multiple-Path Particle Dosimetry (MPPD) model to estimate the deposition fraction. MPPD is a widely used, fast-running, GUI-driven,

Java-based set of algorithms that can calculate the deposition and retention of both mono-dispersed and poly-dispersed particulates and aerosol droplets in human respiratory tracts (please see Asgharian 2006a, Asgharian 2006b, Asgharian 2006c for complete details). The human respiratory model includes both single-path, symmetrical calculations as well as several multi-path variations of limited-asymmetric, asymmetric and stochastic models. The limited-asymmetric model uses a 5-lobed model with subsequent symmetric airways. An age-dependent set of lung morphologies is also available. The model can calculate deposition in three regions, extrathoracic (ET), tracheobronchial (TB) and pulmonary (P), or by specific airway generation, shown in Figure 4. Clearance pathways and timeframes are significantly different in these different regions and since americium is only moderately soluble, the estimated fractional deposition in these regions can significantly impact the projected clearance, uptake, and resultant radiation dose. Therefore, precise deposition calculations are critical in making accurate estimations in the americium model.

Since MPPD does not rely entirely on a simple, symmetrical model, such as that used in the International Commission on Radiological Protection (ICRP) Publication 66 (1994), the model can account for specific lobal deposition in the asymmetric model as well as generation-by-generation deposition throughout the respiratory tract. Results of the deposition and retention calculations using MPPD have been favorably compared with experimental data from both rats and humans (Raabe 1976, Heyder 1986). Results were published that indicate the asymmetrical model used in the MPPD is effective at modeling clearance (Asgharian 2001). In addition, MPPD includes a set of stochastically generated lung models that can be used to provide an estimate of the uncertainty associated with respiratory tract deposition.

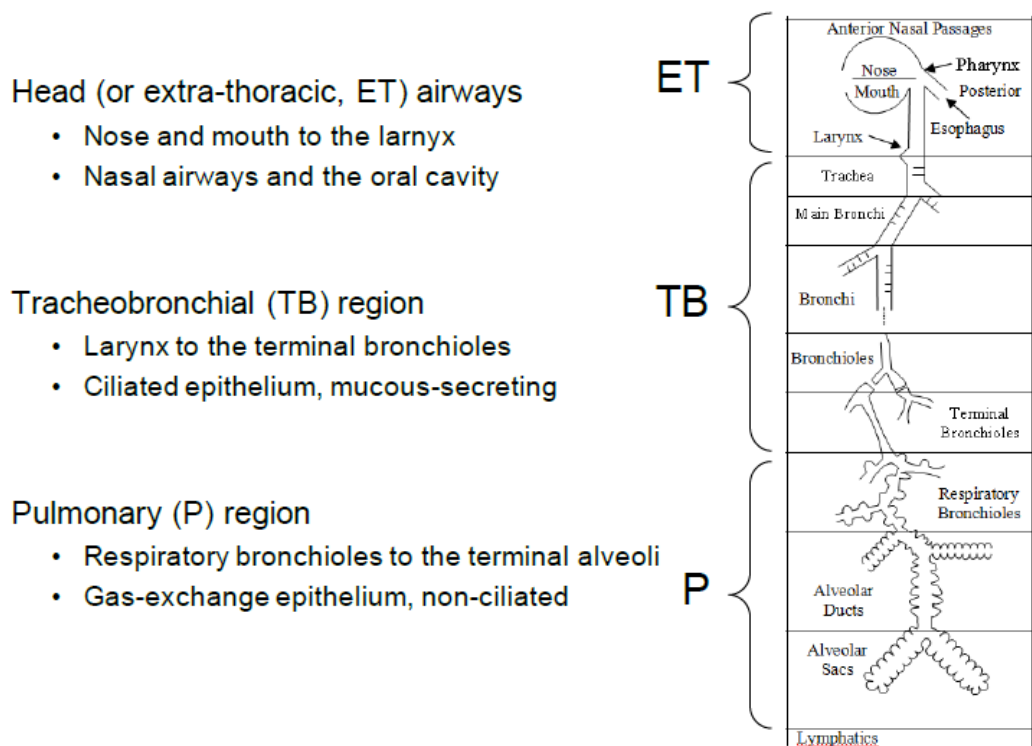


Figure 4. The Three Functional Regions of the Respiratory Tract (Asgharian 2006a)

As an example, we noted earlier that in an area with an ambient wind of 4 m/s, approximately 60% of particles of 22 microns would be inhaled. Using MPPD, we calculated that of the particles inhaled, approximately 94% would deposit in the ET region, 5.4% would deposit in the TB region and 0.0002% would deposit in the pulmonary region, and the remaining 0.59% exhaled without depositing.

In much of the published data, 5 micron particles are used as a standard for inhalation exposure scenarios. In cases with 5 μm particles, 100% of the particles would be inhaled. Based on MPPD calculations, we calculate that approximately 31% would deposit in the ET region, 39% would deposit in the TB region and 30% would deposit in the pulmonary region, assuming a breathing rate of 20 L/min.¹

Additional example outputs from the inhalation model are provided in Appendix A.

4.2.5. Respiratory Clearance and Systemic Uptake

Studies indicate that absorption of americium from the lungs can range to from fast to slow. Absorption depends on many factors, including: the chemical form, type and size of particles the americium is associated with, the presence of other similar nuclides, such as plutonium, and the region where the particles are deposited. In general, AmO_2 is considered a moderately soluble compound that exhibits moderately fast uptake according to ICRP (1994). The ICRP offers a generic uptake model for compounds that exhibit moderate solubility, delivering a moderately fast uptake from the respiratory tract. The ICRP model indicates that 10% of the material is rapidly absorbed with a half-time of about 15 minutes and the remaining material clears slowly with a half-time of about 200 days.

Conversely, case studies of human exposures (Sanders 1974, Fry 1976, Newton 1983, Rosen 1983) and experimental animal data (Mewhinney 1982a, 1982b, 1983; Griffith 1983) indicate that a very rapid early clearance of the inhaled material does not happen. Research shows a delayed peak clearance at about 3 weeks post-exposure occurs for approximately 80% of the deposited material. Additionally, as evidenced by bioassay of fecal excretion, long-term clearance from the pulmonary region is predominately through the GI tract. Intermediate clearance involves some transfer of material from the lymph system, which eventually releases it to the blood. Based on the collective data, a modified model of respiratory clearance and absorption from the respiratory tract was proposed by Leggett (Leggett 1992). We implement Leggett's uptake model, since it was based on Am-specific data. Leggett's model will be more precise than the generic ICRP model (ICRP 1994) with the exception of the fast transfer from the pulmonary region to the systemic circulation, which is justified below. The parameters used for the uptake model are listed in Table 1. Implementation of these parameters and a complete mathematical description of the model are provided in Appendix B.

The deposition fractions obtained from MPPD determine the amount of material in each of the three main regions. The fraction of material cleared from the different respiratory regions into the GI tract or absorbed into the blood will transfer according to the corresponding half-times in the table. Note that all of the deposition into the ET and TB regions is cleared via the GI tract. The portion absorbed into the blood from the pulmonary region will be added directly into

¹ The breathing rate (20 L/min, average breathing rate for a worker) and particle size (5 micron) were chosen for scenario calculations so that comparisons could be made with other published data that use these parameters (ICRP 1994, NCRP 2009b).

the blood compartment (systemic circulation) of the Am biokinetic model described in the next section.

Table 1. Respiratory Clearance and Uptake Parameters

| Deposition Region | Clearance mode; Transfer to: | Fraction of transfer to each mode | Half-time of transfer | Deposition fraction of 5µm particles |
|--------------------------|-------------------------------------|--|------------------------------|---|
| Extrathoracic | Blood | 0 | - | |
| | GI tract | 1 | 0.4 days | 0.31 |
| Tracheobronchial | Blood | 0 | - | |
| | GI tract | 1 | 0.2 days | 0.39 |
| Pulmonary - 1 | Blood | 0.72 | 3-40 days | |
| <i>fast</i> | GI tract | 0.16 | 11 days | 0.30 |
| Pulmonary - 2 | Blood | 0 | 0.5 yrs | |
| <i>intermediate</i> | GI tract | 0.17 | 0.5 yrs | |
| Pulmonary - 3 | Blood | 0.006 | 3 yrs | |
| <i>slow</i> | GI tract | 0.024 | 3 yrs | |

Studies in beagles show that the fast pulmonary clearance (Pulmonary – 1 in Table 1) and associated half-time is highly dependent on particle size (Mewhinney 1982, 1983). Larger particle size is associated with slower dissolution; therefore, the half-time for the transfer of americium from the pulmonary-1 region to the systemic circulation can be described as a function of particle size. The data from beagles are well correlated with the limited data available from humans (Mewhinney 1983). To more accurately describe the absorption, the following particle size-dependent function based on the data published in Mewhinney 1983 is implemented:

$$T_{1/2} = (14.19 * PS) - 3.5$$

where $T_{1/2}$ is the half-time for the fast transfer of Am from the pulmonary region to the blood and PS is the particle size in microns. If particle size is not known, a default value of 1 or 5 microns may be used. For polydispersed particle exposures, an average particle size provides a reasonable approximation.

It is important to note that particle size significantly impacts both:

- the distribution in the respiratory tract, which dictates the amount of americium reaching the pulmonary region for absorption into the blood and,
- the rate of absorption of americium into the blood from the pulmonary (thus, clearance from the lung).

In most human exposures, the particle size of the exposure has not been known; a large variability exists in the data available on humans. Comparisons with case studies are particularly

challenging, since americium absorption from the lung has delayed components and the observed biokinetics are dictated by the precise exposure conditions.

4.2.6. Uptake from the GI Tract

The portion of americium transferred to the GI tract is primarily excreted directly through fecal elimination, although a small fraction of the Am can be absorbed into the systemic circulation from the GI tract. In case studies and experimental studies, americium has exhibited very limited absorption from the GI tract. According to human data (from Sellafield releases (Hunt 1986) and from animal data (Sullivan 1985)) from individuals who consumed seafood contaminated with Am-241, 0.004-0.03% of americium absorption from the GI tract was observed with a central estimate of 0.01%. A value of 0.05% absorption was adopted by the ICRP (1993) for all actinides. For the americium-specific model developed in this work, a conservative value of 0.02% for gastrointestinal absorption, as proposed by Leggett (1992), will be used.

4.3 Americium Biokinetic Model

The distribution of americium throughout the body's tissues is calculated according to an americium-specific biokinetic model developed by Leggett (1992) and modified by ICRP (1993), as shown in Figure 5. The modifications made by ICRP include adjustments to the transfer coefficients for the different bone compartments for a single value for the average adult. The biokinetic model is based on transfer coefficients, detailed in Table 2.

The physiologically-based model developed by Leggett was chosen because it is the most detailed model available for americium. The model allows more detailed and accurate dosimetry calculations for the whole body and enables the calculation of doses to specific tissues. Specific tissue doses are critical in determining acute effects from radiation for which dose to critical organs must be examined. Detailed tissue transport data obtained from the biokinetic model also enables the calculation of the amount of americium available for removal by DTPA treatment.

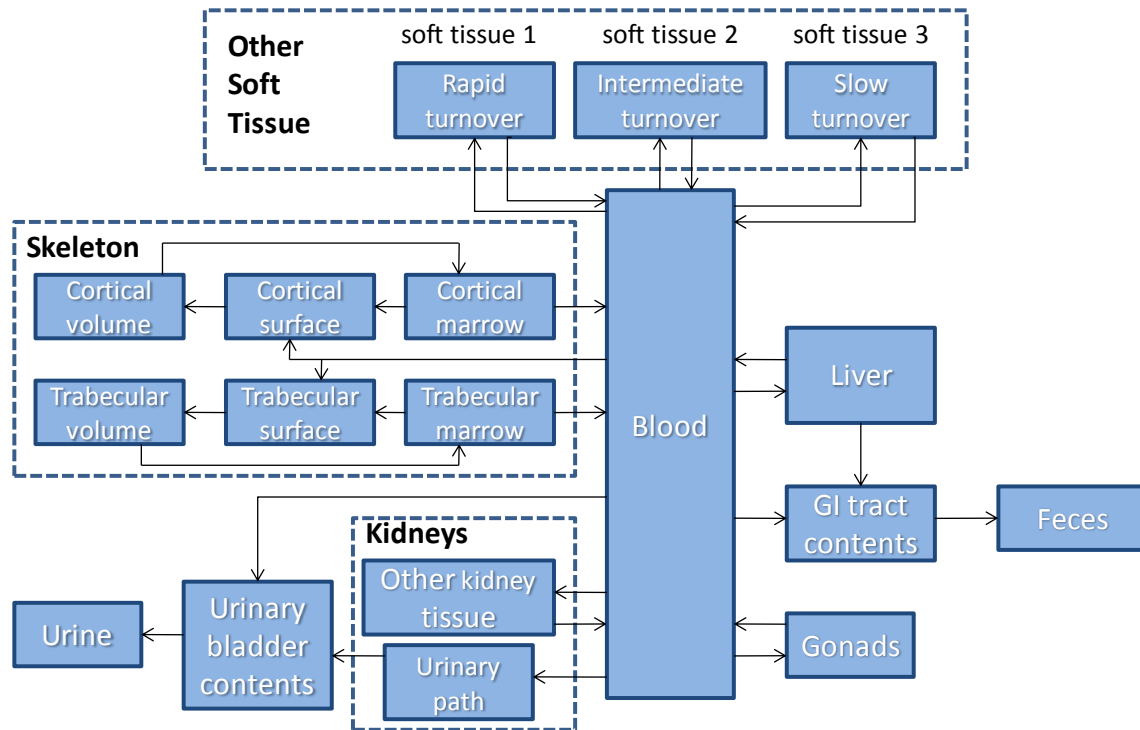


Figure 5. Americium Biokinetic Distribution Model (Leggett 1992, ICRP 1993)

The Am biokinetic model obtains input from the inhalation model to ascertain the amount of americium entering the bloodstream from the respiratory tract, either by direct absorption into the blood or indirect respiratory clearance to the GI tract and subsequent absorption (which contributes minimally).

4.3.1. Transfer Coefficients for Americium

The Am biokinetic model allows incomplete, tissue-dependent extraction of material during passage through the circulation and return of material from tissues to blood. The model performs this function by accounting for the blood flow rate to different tissues, estimated tissue retention times, and subsequent transfer coefficients.

Table 2. Transfer Coefficients (Leggett 1992, ICRP 1993)

| From | To | Transfer coefficient (d⁻¹) |
|--------------------|--------------------------------|--|
| Blood | Liver | 11.645 |
| Blood | Soft tissue 1 | 10.0 |
| Blood | Soft tissue 2 | 1.67 |
| Blood | Soft tissue 3 | 0.466 |
| Blood | Cortical surfaces | 3.49 |
| Blood | Trabecular surfaces | 3.49 |
| Blood | Kidneys 1 | 0.466 |
| Blood | Upper large intestine contents | 0.303 |
| Blood | Kidneys 2 | 0.116 |
| Blood | Testes | 0.0082 |
| Blood | Ovaries | 0.0026 |
| Blood | Urinary bladder contents | 1.63 |
| Liver | Blood | 0.00185 |
| Liver | Small intestine contents | 0.000049 |
| Soft tissue 1 | Blood | 1.386 |
| Soft tissue 2 | Blood | 0.0139 |
| Soft tissue 3 | Blood | 0.000019 |
| Cortical marrow | Blood | 0.00760 |
| Cortical surface | Cortical marrow | 0.0000821 |
| Cortical surface | Cortical volume | 0.0000411 |
| Cortical volume | Cortical marrow | 0.0000821 |
| Red marrow | Blood | 0.00760 |
| Trabecular surface | Red Marrow | 0.000493 |
| Trabecular surface | Trabecular volume | 0.000247 |
| Trabecular volume | Red Marrow | 0.000493 |
| Kidneys 1 | Urinary bladder contents | 0.099 |
| Kidneys 2 | Blood | 0.0039 |
| Testes | Blood | 0.00019 |
| Ovaries | Blood | 0.00019 |

The transfer coefficients for the flow of americium from blood to different tissue compartments and its return to the circulation were mathematically derived from the fractional

blood flow to the tissues and knowledge concerning the tissue-specific retention of americium in the compartments. The knowledge is based on human exposure case studies and autopsies, as well as detailed experimental animal studies, which were reviewed by Leggett (1992), ICRP (1993), and NCRP (2009).

4.4 DTPA Treatment Model

Since DTPA is not readily absorbed from the GI tract into the blood stream and little americium is secreted into the gastrointestinal tract, DTPA must be administered intravenously for effective decorporation. Inhaled DTPA may be absorbed up to 20% from the lung into the systemic circulation and is a potential mode of administration. Based on animal studies and one human tracer study using ^{14}C -labeled DTPA, the chelate uniformly distributes throughout the body via circulation; remains in the extracellular space; is not metabolized to any significant degree (Volf 1978, Stather 1983). A basic biokinetic model for DTPA is shown in Figure 6. Since DTPA does not concentrate in any specific tissues or transfer to intracellular space, it removes americium by chelating Am in the systemic circulation (i.e. the blood compartment of the Am biokinetic model). The process of decorporation is limited by the rate of mobilization from the lungs to the circulation and the rate of release of americium back into the circulation from tissues that have sequestered it, such as the liver and bone. While the americium biokinetic model calculates the amount of americium in the circulation at any given time, the DTPA biokinetic model calculates the amount of DTPA in the circulation at any given time. Since the recommended dose of DTPA results in a vast excess of DTPA in the circulation as compared to the amount of americium in the circulation and the binding affinity of DTPA for Am is quite strong, we can assume that all of the Am in the blood stream will be bound by DTPA during its circulation and is subsequently removed by renal clearance.

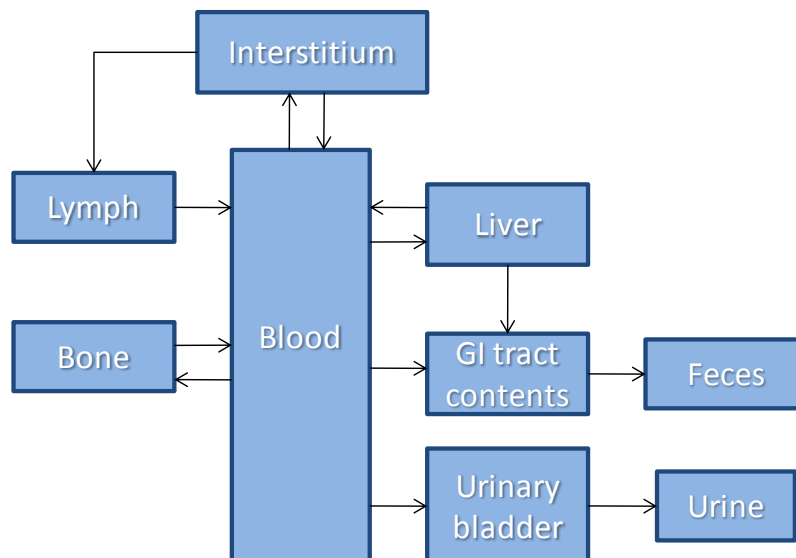


Figure 6. DTPA Biokinetic Model

4.4.1. Route of Administration

The primary route of administration for DTPA is intravenous administration and is considered a fixed parameter in the model (FDA 2004). This route of administration will quickly reach an equilibrium concentration of DTPA in the circulation.

4.4.2. Formulation, Dose, and Time Course

Ca- and Zn-DTPA are formulated in a 5 ml hyperosmolar solution, containing 1 gram of the respective salt adjusted to physiological pH, with sodium hydroxide provided in sterile, non-pyrogenic ampoules suitable for intravenous administration (FDA 2004, Hameln 2004). This is a standard formulation, which is a fixed parameter in the treatment model.

Although nebulized DTPA may be administered with an inhaler, there is insufficient data to adequately model this route of administration. The evidence that is available does not indicate any improved chelation for AmO₂ from this route of administration (Ménétrier 2005). In addition, nebulized chelation therapy may exacerbate asthma (Hameln 2004); therefore, intravenous injection is the preferred method of treatment and is treated as a fixed parameter in the model.

The optimal dosing regimen for an adult is 1 g of Ca-DTPA on the initial day of treatment followed by 1 g Zn-DTPA per day for subsequent treatments, until the radionuclide burden is adequately reduced (FDA 2004). The transition from Ca-DTPA to Zn-DTPA is recommended due to toxicity issues and is briefly discussed later in this report. The model assumes that the recommended dosing regimen is followed, although the mathematical implementation of the decorporation model, as described below; cannot discriminate between Ca- and Zn-DTPA.

The duration of treatment, in days, is an input variable for the treatment model. The effect of treatment duration can be examined with the model, with longer treatment courses having a greater impact on total radiation dose.

4.4.3. Time from Exposure to Treatment

The time from exposure to initiation of treatment is an input variable parameter in the model. Using the americium biokinetic model enables the dose calculation to be made as a function of Am-241 concentration in the body integrated over time. When DTPA treatment begins, americium concentration is reduced from the systemic circulation (the blood compartment). Re-equilibration is achieved over time according to the tissue transfer coefficients in the biokinetic model. Since radiation dose is calculated based on the americium concentration as a function of time, it can be calculated seamlessly using the model, regardless of DTPA treatment start time or duration. The impact of time from exposure to initiation of treatment can be examined with the model. The greatest impact on dose reduction is observed when treatment begins soon after exposure. This is particularly important for americium, as it is absorbed into the bloodstream, where it can be sequestered by the liver and incorporated into bone, which is particularly difficult to mobilize.

4.4.4. Americium Decorporation

The binding affinity of DTPA for Am is quite strong, as demonstrated by its stability constant of 22.9, at physiological conditions (Volf 1978, Anderegg 2005). The stability constant is the equilibrium constant for the formation of a metal complex (a chelate bound to a metal) in a

solution and reflects the affinity a chelate has for a specific metal. For comparison, the stability constant of DTPA with calcium is about 2 and for zinc about 4 (Anderegg 2005). Thus DTPA will more readily exchange zinc or calcium ions, allowing for the opportunity to bind to americium. DTPA binding of americium is stronger than with other competing metal ions and DTPA does not readily release americium once it is bound.

As described above, the recommended dose of DTPA results in an initial vast excess of DTPA in the circulation as compared to the amount of americium in the circulation. Given the strong affinity of DTPA for Am and its excess, we can assume that all of the Am in the blood stream will be bound by DTPA during its circulation and subsequently removed by renal clearance.

For each DTPA treatment, the total amount of americium entering the circulation (blood compartment) from all contributing tissues is integrated over the established “effective” residence time, to determine the total americium bound or sequestered by DTPA for each treatment. An additional removal mechanism for Am under DTPA treatment was added to account for an initial spike in urinary excretion caused by DTPA treatment, representative of Am removal from the interstitial space of the tissues. The amount of Am sequestered (bound) by DTPA is deducted from the total body-burden of americium and added to the amount of Am excreted. The americium remaining in the tissue compartments is then re-equilibrated according to the Am biokinetic model. The effective residence time refers to the period of time that DTPA can efficiently remove americium from the body. The effective residence time and interstitial removal were developed as described below.

4.4.5. Optimizing DTPA Effective Residence Time

Different effective residence times for americium in the circulation (i.e. blood compartment) were examined in the treatment model. The model (described above) is constructed such that all of the Am entering the blood compartment during the effective residence time for DTPA, after administration, is removed. The rate of Am sequestered from the circulation during DTPA treatment is the sum of Am in the blood that would normally move to tissue compartments, and the amount of Am being released from each organ back into the circulation, over the specified effective residence time for each treatment:

$$\frac{d}{dt}(Am_{Sequestered}) = \sum (Am_{blood} * TC_{blood \rightarrow organ_i} + Am_{organ_i} * TC_{organ_i \rightarrow blood})$$

where $Am_{Sequestered}$ is the amount of Am chelated by DTPA, Am_{blood} is the amount of Am in blood, Am_{organ_i} is the amount of Am in each organ (or tissue) compartment that will transfer within the blood (see Figure 5), and TC is the transfer coefficient (in units per day; Table 2) for the respective flow of Am.

The transfer in and out of the blood during untreated periods is represented as:

$$\frac{d}{dt}(Am_{blood}) = \sum -Am_{blood} * TC_{blood \rightarrow organ_i} + Am_{organ_i} * TC_{organ_i \rightarrow blood}$$

The transfer during treatment changes to:

$$\frac{d}{dt}(Am_{blood}) = \sum -Am_{blood} * TC_{blood \rightarrow organ_i}$$

Americium retention under DTPA treatment was examined assuming a maximum residence time of 24 hours, based on the biokinetic model for DTPA (Stather 1983). Data was generated on effective residence times for DTPA ranging from 2 to 24 hours, as shown in Figure 7. For this scenario, treatment was initiated on day 2 after exposure to 5 micron particles. Treatment was continuous for 30 days. The simulation shows how effective continuous treatment can be when initiated early. In this scenario, americium is removed nearly as soon as it enters the bloodstream. Since a slower absorption of Am into the blood occurs as particle size increases, DTPA treatment can be very effective if administered early (before americium becomes lodged in the bone and liver) and continuous. Also, since Am moves into the bloodstream relatively slowly, different effective residence times for Am do not have a large impact on the amount of Am that can be removed with each treatment.

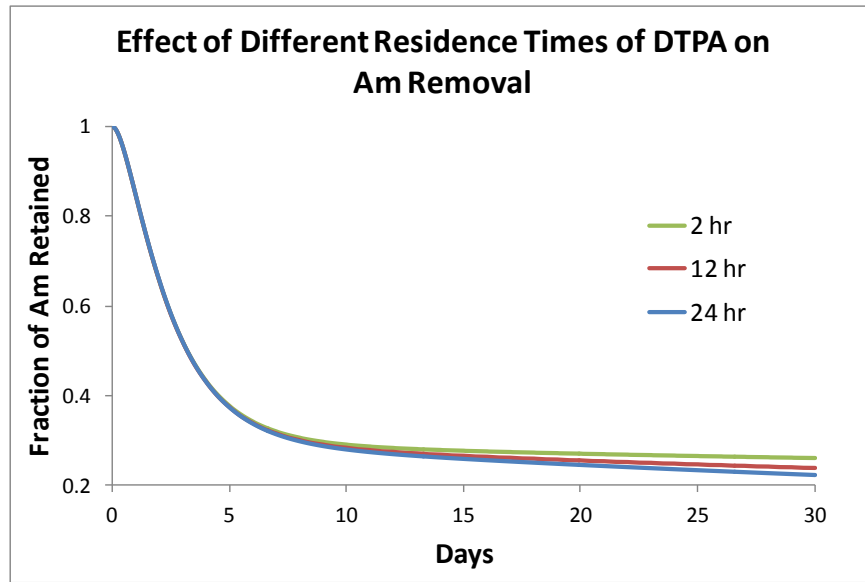


Figure 7. Effect of Different Effective Residence Times for DTPA in the Blood

Using the Am biokinetic and decorporation model, the maximum effective residence time for 24 hours provides an initial increase of approximately 10 times the urinary excretion of Am. DTPA has been reported to increase initial urinary excretion of Am 18-fold (subsequently declining to approximately 4-fold) when treatment is initiated months or years after exposure (Fasiska 1971, Rosen 1980). Other case studies indicate a dramatic initial increased excretion of Am, ranging from 50 to 140-fold (Whalen 1972, Cohen 1979, Roedler 1989); however, the chemical form of americium was not reported in those studies. The dramatic initial increase in excretion could have been related to exposure to nitrate or citrate salts of americium, which are more readily absorbed and easily removed by chelation therapy. However, in all cases, excretion upon DTPA treatment declines to a more steady-state removal of Am after a period of time.

Recent studies on the treatment of plutonium and americium with DTPA in animal models indicated that DTPA can effectively remove actinides from tissues in the extracellular/interstitial space and possibly competitively bind nuclides from cellular surfaces (Phan 2005, 2006a, 2006b; Fritsch 2008, 2009, 2010). Based on these studies' findings, researchers hypothesized that a small amount of DTPA can actually enter intracellular spaces and bind to and remove actinides. This intracellular attachment mechanism is plausible and can explain the observation of a continued elevated excretion for a period of time after treatment ends. Although the vast majority of DTPA clears the blood in 24 hours (99.9%), a small amount of DTPA clears more slowly (Stather 1983) and therefore this hypothesized mechanism needs to be validated. Sufficient evidence exists to support interstitial removal of actinides via DTPA treatment; however, all of the reported studies were conducted on soluble species of plutonium and americium.

DTPA treatment via chelation in the interstitial space showed an elevated increase in Am excretion. To account for the removal of interstitial Am (from americium oxide exposure), approximations were made by using existing transfer coefficients from the different tissue compartments and estimating an interstitial removal fraction (IRF). The IRF is based on observed excretion from both human case studies (Rosen 1980, Sanders 1974) and animal model experiments using inhaled AmO₂ exposures (Muggenburg 1983, Guilmette 1989). The transfer coefficients represent the binding affinity of different tissue compartments for Am. Each compartment could be further divided into an interstitial and cellular component, each with separate transfer coefficients. However, since no data exist at this level, the fraction of americium that can be mobilized from the interstitial space must be approximated. The interstitial removal from each tissue is described mathematically as:

$$\frac{d}{dt}(Am_{organ_i}) = Am_{blood} * TC_{blood \rightarrow organ_i} - Am_{organ_i} * TC_{organ_i \rightarrow blood} - Am_{organ_i} * TC_{organ_i \rightarrow blood} * IRF$$

where *IR* is a factor that accounts for the interstitial removal of americium.

The rate of Am sequestration expands to:

$$\begin{aligned} \frac{d}{dt}(Am_{sequestered}) &= \sum (Am_{blood} * TC_{blood \rightarrow organ_i} + Am_{organ_i} * TC_{organ_i \rightarrow blood} + Am_{organ_i} * TC_{organ_i \rightarrow blood} \\ &\quad * IR) \end{aligned}$$

The case study reported by Rosen et al. is examined using the model (Rosen 1980). This case study involves an inhalation Am exposure, which was not detected for over two years; therefore, particle size dependence of the deposition and early redistribution from the respiratory tract do not interfere with examining the impact of treatment on urinary excretion. A model simulation is run for an exposure to 1 micron particles occurring two years before treatment with DTPA begins. The daily excretion rate before treatment and two days after treatment is compared, to obtain an excretion enhancement factor (EEF; treated daily urinary excretion rate / untreated

daily urinary excretion rate). These values are compared to the initial excretion enhancements observed after treatment initiation from the case study.

Table 3. Impact of Interstitial Removal on Excretion

| | EEF |
|-------------------|------------|
| Rosen 1980 | 18.2 |
| Model without IR | 10.4 |
| Model with IR=0.5 | 16.6 |
| Model with IR=1 | 22.0 |
| Model with IR=2 | 32.5 |

As an approximation, an interstitial removal factor of 1 was chosen for further validation comparisons. The decorporation model then is used to compare results with other studies. One case study in which an inhalation exposure to mixed oxides of Am-241 and curium-244 (Cm-244) was examined (Sanders 1974). Intermittent administration of DTPA occurred from day 50 to day 113 post-exposure. In this case, the EEF after each treatment was estimated to range from 10 to 19. Model results simulating the exposure (assuming 5 micron particle exposure and breathing rate of 15 L/min) provided an EEF of 13, including the IRF of 1. An EEF of 10 is obtained from the simulation without accounting for interstitial removal. Accounting for interstitial removal provides a better average representation of the data in this case study. However, one must note that this case study involved mixed nuclides. Although americium and curium have similar biokinetic models, they are not identical and therefore only a rough comparison can be made from these data.

Data from animal studies were also evaluated to determine how well the model predicts tissue retention with and without treatment. The parameters from beagle dog studies (Muggenburg 1983, Guilmette 1989) were simulated with the model (1.2 micron particle exposure, 15 L/min breathing rate). Americium retention at 64 days post exposure (reported as percent initial intake) in the whole body and select tissues are compared in Table 1. The animal study and the simulation initiated DTPA treatment at 1 hour post-exposure. The simulated data provide reasonable comparisons to the animal data (variability due to the differences in species has not been accounted for) with whole-body retention with and without treatment in good agreement. There was no effect on interstitial removal in these simulations (i.e. the results with no IRF or an IRF of 1 were not significantly different). Treatment started only one hour after the exposure and continued for the duration of the experiment (or simulation), does not provide enough time for americium to concentrate and reach equilibrium in any of the tissues.

Table 4. Comparison of Americium Retention (% Intake) at 64 Days in Beagles and in Model Simulation

| | Beagle Study (% Intake) | | Model Results (% Intake) | |
|------------|-------------------------|----------------|--------------------------|----------------|
| | <i>Untreated</i> | <i>Treated</i> | <i>Untreated</i> | <i>Treated</i> |
| Lung | 24.5±2.5 | 15.4±5.9 | 19.3 | 19.3 |
| Liver | 25.1±3.4 | 1.17±0.8 | 34.3 | 0.03 |
| Bone | 21.8±4.2 | 4.03±0.05 | 22.3 | 0.02 |
| Total Body | 76.7±7.8 | 22±7.2 | 81 | 19.5 |

The three comparisons above indicate that accounting for interstitial removal with an IRF of 1 provides reasonable approximations of DTPA removal of americium for scenarios that start treatment soon after exposure, as well as those with long delays in treatment initiation.

It is worth noting that a decline in the enhanced excretion is observed over time as tissue reservoirs with faster transfer coefficients (reflecting tissues that bind Am less tightly) are depleted. Therefore, the excretion enhancement obtained from DTPA declines. Case studies show that upon cessation of treatment whole-body re-distribution of Am from slower tissue transfer compartments occurs and other soft tissue levels rise upon re-equilibration. Therefore, protracted treatment with DTPA is sometimes necessary for more effective DTPA treatment. The current model code is constrained by the software used (see section 4.1), such that scenarios with protracted treatments are not easily evaluated. Future implementation will include this feature.

4.4.6. Toxicity/Side Effects

Treatment with DTPA can deplete endogenous metals, which is why the Zn salt is preferred for long-term treatment. However, other endogenous metals may be depleted if treatment spans several months. During prolonged treatments serum levels of essential metals should be monitored accompanied by the use of mineral replacements, as needed. Otherwise, DTPA has not been reported to have any significant adverse effects. Approximately 6% of patients in the registry of DTPA-use reported side effects, such as headache and lightheadedness. The use of nebulized DTPA for inhalation dosing has been reported to cause coughing and wheezing in patients and can exacerbate asthma (FDA 2004, Hameln 2004).

Note that Ca-DTPA is considered Pregnancy Category C and Zn-DTPA considered Pregnancy Category B (Meadows 2001); therefore treatment of pregnant women should begin and continue with Zn-DTPA. Studies to determine if Zn-DTPA is excreted in breast milk have not been conducted, but Ca-DTPA can be expected to appear in milk. Because many radionuclides are known to be excreted in varying degrees in breast milk, it is recommended that women with internal deposition of radionuclides not breast feed, whether or not they are receiving chelation therapy (NCRP 2008).

Patients with renal impairment do not need dose adjustment; however, if renal insufficiency or renal failure is present, Ca-DTPA should not be used. If patients with renal impairment are

heavily contaminated, using dialysis increases the rate of elimination. Dialysis fluid will become radioactive and appropriate radiation safety measures should be instituted (NCRP 2008).

Although long-term treatment with Zn-DTPA in healthy adults does not cause any serious side effects, the route of administration is through I.V. injection. This is, to some degree, invasive under continuous treatment and must be considered in the overall treatment regimen adopted.

4.5 Radiation Dose Model

The radiation dose delivered to the critical target organs (red bone marrow and lungs) for acute effects must account for the americium burden in each of the tissues. The amount of energy absorbed in the critical target organ must account for the energy emissions from all sources. The method used for this calculation is sometimes referred to as the Medical Internal Radiation Dose (MIRD) method. The method utilizes tabularized data that are computational estimates of the amount of energy deposited in a specific organ, based on the amount of energy emitted from radioactive material within another organ (Snyder 1978). Due to the complex nature of the human anatomy, these specific absorbed fractions (SAFs) in each of the tissues require detailed radiation transport calculations, as described below. The dose to specific target organs requires an integrated calculation, based on the dose rate as a function of time, resulting from the time-dependent Am-241 body-burden. Since Am-241 emits both a low-energy photon and an α -particle, the dose to the red bone marrow and lungs will include contributions from photons emitted from all organs. Also, Am within the red bone marrow and lungs will further emit photons and α -particles.

The local energy deposition from the α -particle is modified by a Quality Factor of 20 to convert to dose equivalent. The high linear energy transfer (LET) of the α -particle causes a higher level of localized damage than a low LET energy deposition from photons. To quantify the increase in potential biological damage, multiply the energy deposition by a Quality Factor (QF). For α -particles in the 5 MeV range, the accepted QF is 20 (ICRP 1991).

In addition to the organ-specific dose calculation, we present a method for approximating the 50-year committee effective dose equivalent (CEDE). The CEDE is the dose calculation that is commonly used for radiation protection associated with internal hazards and it is also the unit upon which most long-term complications or cancer incidence rates are based. Acute dose calculations are generally considered to be associated with the dose accumulated over the first thirty days; the majority of the total dose accumulated will occur during this time period. The body-burden, and the associated dose accumulation rate, will decrease with time as a result of radioactive decay, natural elimination and accelerated elimination resulting from DTPA treatment.

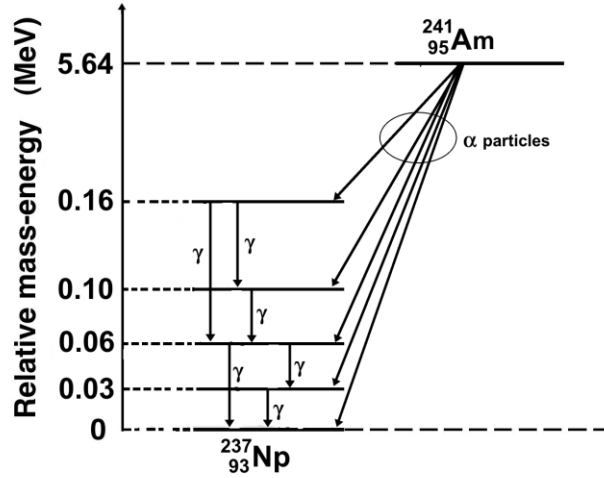


Figure 8. Decay Scheme for Am-241

4.5.1. Organ-Specific Acute Doses

The decay scheme illustrated in Table 8 shows all of the decay paths for Am-241. The predominant mode of decay for Am-241 is with a 5.6 MeV (average energy) α -particle emission and a 60 keV photon to neptunium-237. Since the americium will be distributed by the bloodstream to most organs throughout the body, determining how much energy is absorbed by specific organs is complex. The dose delivered to each given organ is a result of energy emitted from all organs, including self-absorption in the same organ. High-fidelity phantoms were created to facilitate calculating these doses and both Monte Carlo and discrete calculation methods were implemented. Oak Ridge National Laboratory (Christy 1987a) generated a set of Specific Absorbed Fractions (SAFs) that provides an energy-dependent means of calculating the dose absorbed by an organ, as a function of the energy emitted by another organ. For example, and average decay of an Am-241 atom emits a single 5.6 MeV α -particle. In addition, Am-241 decay emits a 60 keV photon 36% of the time. Therefore, for every Becquerel (1 disintegration per second) of activity in a given organ, the 5.6 MeV of energy from the alpha particle and 21.6 keV (on average) of photon energy is emitted per second. By interpolating the SAF tables, the fraction of the energy, from a given emission, deposited in another (or the same) organ can be calculated. The contributions from all organs to a specific target organ are summed. For Am-241, the red bone marrow and lungs are considered the most critical target organs for predicting acute radiation effects, specifically hematopoietic syndrome and pneumonitis leading to lung fibrosis. As an example, the calculation for the red bone marrow dose is summarized in the following equation:

$$D_{BM}(t) = \sum_{t_0}^t \left[\sum_{i=1}^N \left(\frac{A_{Am,t}^i \cdot \bar{E} \cdot SAF(O_i \Rightarrow BM)}{M_{BM}} \right) \right] \cdot \Delta t$$

$D_{BM}(t)$ = Dose delivered to bone marrow at time t
 $A_{Am,t}^i$ = Activity of Am in organ i as a function of time
 \bar{E} = Average energy emitted per decay
 where: Δt = Time step increment
 $SAF(O_i \Rightarrow BM)$ = Specific Absorption Fraction from Organ i to bone marrow
 M_{BM} = Mass of bone marrow

For calculating the dose to the lungs, the same equation applies, but substituting the SAF values for the lungs and the mass of the lungs.

The SAF values for the 60 keV photon are shown in Table 5 for each source organ, with the red bone marrow or lungs as the target organ. Some assumptions were necessary to harmonize the SAF values given by Christy (1987) with the americium tissue content provided by the Leggett (1992) model. For the three soft tissue compartments, SAF values for the skin, heart, and spleen represent soft tissues 1, 2, and 3, respectively. More detailed SAF values for the lungs and GI contents were available (for example SAF values are available for each piece of the GI tract) than the number of compartments in the biokinetic model. As a result, conservative estimates were chosen, using the highest compartment values to provide an upper estimate of dose. For the more detailed bone compartments in the biokinetic model, only one SAF value is available for each of the cortical and trabecular bone compartments. Therefore, the same SAF is applied to each of the cortical bone components in the biokinetic model.

Table 5. Photon SAF Values for Am-241 for Red Bone Marrow (RBM) and Lungs

| Source Organ | SAF Values - RBM | SAF Values - Lungs |
|--------------------------|------------------|--------------------|
| Blood | 0.0048502 | 0.006654 |
| Lungs | 0.0059631 | 0.086053 |
| Liver | 0.0037922 | 0.014245 |
| Kidneys | 0.0084895 | 0.003258 |
| Urinary bladder contents | 0.0033358 | 0.000018086 |
| Cortical bone | 0.01132 | 0.0038441 |
| Trabecular bone | 0.026774 | 0.0064634 |
| Red marrow | 0.026774 | 0.0064634 |
| GI contents | 0.012101 | 0.0067601 |
| Soft tissue 1 | 0.0020986 | 0.0023769 |
| Soft tissue 2 | 0.0052441 | 0.034344 |
| Soft tissue 3 | 0.0041667 | 0.0113388 |
| Testes | 0.00091229 | 3.0374E-06 |
| Ovaries | 0.011548 | 0.000083631 |

The mean free path of a 5.6 MeV α -particle is measured in microns. Thus, it is assumed that the alpha particles will deposit all of their energy exclusively within the organ of uptake. The red bone marrow is a complicated case because of the intricate nature of the structure in and around the blood forming region, the model assumes the α -particle energy is deposited locally in the portion of bone structure where the americium is retained. Therefore, for the red bone marrow and the lungs, it is assumed that all of the alpha particles deposit all of their energy within those organs.

4.5.2. Effective Whole-Body Equivalent

While it is imperative to understand doses to specific organs for acute effects, most predictors of long-term effects, such as cancer induction from internally deposited radioactive material, are based on the concept of a 50-year committed whole-body dose. In other words, the model considers the radiation dose that the body will accumulate over a 50-year period, following the uptake. This dose value is based on the estimated dose delivered to specific organs or tissues. The resultant dose is then multiplied according to a specified tissue weighting factor (ICRP 1991). While our model approximates the calculation of dose to a specific organ as a function of activity in other organs, performing this calculation from all organs, to all organs, and appropriately weighting the results is not practical; SAF values are not available for all tissue contributions in the biokinetic model. Too many assumptions would be required for the calculation, and the resulting uncertainty in this calculation would be significant. However, we approximate the dose using tabulated estimates of 50-year committed doses from inhalation uptakes of Am-241. By using some basic assumptions, we developed a method for the incremental accumulation of whole-body equivalent dose, thereby estimating the whole-body effective dose over time and the 50-year committed dose.

The NCRP estimates a 50-year effective dose equivalent of 2.7E-05 (Sv/Bq) (NCRP 2009b) for inhalation of 5 micron Am-241 particulates. We can show the accumulation of this dose from the following equation:

$$D(50) = \int_0^{50} \dot{D}(t) dt$$

We can approximate this equation with:

$$D(50) \approx \sum_{i=1}^N \dot{D}(t_i) \cdot \Delta t_i$$

where:

$$\dot{D}(t) = \text{Dose rate at time } t$$

If we assume the dose rate at time t is proportional to the amount of Am-241 in the body at time t , then we can rewrite the previous equation to:

$$D(50) \approx \sum_{i=1}^N C \cdot A_{Am}(t_i) \cdot \Delta t_i$$

where:

$$A_{Am}(t_i) = \text{Americium activity retained at time } t_i$$

$$C = \text{Constant to convert } A_{Am} \text{ to dose rate}$$

Assuming inhalation results in 100% retention; we use this retention equation and assume the americium delivers a “dose equivalent rate” proportional to the amount of americium retained in the body at time t . We further assume the americium is in equilibrium throughout the body at all times. In other words, the proportion of americium in any given organ is constant at all times. We then calculate a dose-rate conversion factor. The equilibrium assumption is reasonable for the majority of the 50-year period, except for the period immediately following the uptake. We calculate the proportionality constant, C , by numerically integrating the results from our model of americium distribution with no treatment. Based on the NCRP estimate of 2.7E-05 Sv/Bq for the 50-year committed dose equivalent, then $C = 1.2008\text{E-}08$ Sv/Bq/day.

Using this conversion factor, we can estimate the accumulation of dose equivalent as a function of the americium retained in the body at any given time, regardless of the elimination rate. This allows us to compare accumulated doses with and without DTPA treatment.

4.6 Efficacy

The efficacy of DTPA treatment can be evaluated in terms of overall dose reduction and prevention of acute and long-term health effects. A dose reduction factor is calculated by dividing the absorbed dose, from a given Am-241 intake, with a specified treatment regimen by the absorbed dose from same intake without treatment:

$$\text{Dose reduction factor} = D_{DTPA}/D_o$$

where D_o is the dose without treatment and D_{DTPA} is the dose with treatment.

The efficacy is then calculated by:

$$\text{Efficacy} = 1 - D_{DTPA}/D_o$$

where D_o is the dose without treatment and D_{DTPA} is the dose with treatment.

Section 5.

Preliminary Model Results

The results obtained from the preliminary implementation of the model are presented in this section. Final results may vary upon final implementation in stand-alone code and software, due to the precise numerical solutions used in the final code for the integrations required within the various models.

5.1 Preliminary Implementation

A number of the calculations required in the Am decorporation model involve several sets of differential equations and the integration of values over time. Many of the differential equations are interconnected and certain calculations require simultaneous numerical solutions to provide the appropriate outputs. Therefore, Berkeley Madonna™ v. 8.3.18 software, licensed by Robert Macey and George Oster of the University of California, was used to solve the differential equations contained within the overall model. The integration method used was the 2nd order Runge-Kutta method and a time-step interval of 0.0001 days was employed for most calculations. For 50-year calculations, a smaller time step of 0.05 days was used for optimal model performance.

Final software will have the model coded autonomously from Berkeley Madonna™ and incorporate numerical solutions for the differential equations independently.

5.2 Model Outputs

The Am decorporation model can be used to calculate a number of time dependent parameters. The initial conditions currently assumed are that Am intake is through inhalation with a given air concentration of americium, wind speed, breathing rate, and average particle size. The inhalation and uptake model requires these inputs. If values are not known, default parameters may be used for wind speed, breathing rate, and average particle size. The outputs from this portion of the model describe the levels of americium in tissues or excretion in units, to use as the input dose, and the rate is per day (ex. mCi/day):

- Amount of Am deposition in the three major areas of the respiratory tract
- Subsequent Am in blood, lungs, GI tract, liver, kidneys, six separate bone compartments, red bone marrow, urinary bladder, three soft tissue compartments, testes (or ovaries)
- Total Am retained in the body
- Am excretion in urine and feces
- Total Am excreted

Certain tissue values are used as input parameters for the radiation dose calculations. For radiation dose calculations, the input dose must be in radioactive units (e.g. μCi) providing an output in absorbed radiation dose (μGy or μSv). If mass is used as the input, the specific activity of the exposure material can be used to convert the input into activity. The lung and red bone

marrow calculations are derived from the summation of the high and low LET dose contributions from relevant target organs using SAFs as described in section 4.5.1 and integrated over the time period specified. The whole-body effective dose is calculated based on the decay-corrected total americium activity and the constant for the whole-body effective dose over the time period specified, as described in section 4.5.2. The lung and red bone marrow acute doses are used to estimate risk of acute health effects (pulmonary pneumonitis/fibrosis and hematopoietic syndrome) and the whole-body effective dose is used to calculate the 50-year dose for evaluating long-term carcinogenic health risk.

Treatment with DTPA is modeled using the following input parameters: dose of DTPA (1 gram, fixed parameter) material, which results in a vast excess of DTPA in the systemic circulation as compared to Am, treatment start-time relative to the initial intake of americium, and the duration of DTPA treatment. The same model outputs as described above may be calculated with adjustments for the amount of Am-241 sequestered by DTPA during treatment.

Untreated and treated courses, as well as different treatment initiation times and durations, can be evaluated and compared to determine doses and dose reductions that may be obtained in different scenarios. The data generated from different scenarios are detailed below to illustrate the reliability and utility of the Am decorporation model developed in this work.

5.2.1. Impact of Particle Size on Americium Biokinetics and Dose Estimates

As discussed in Section 4.2.5, the particle size or average particle size distribution of the exposure will significantly impact the observed biokinetic profile after an intake. Smaller particle sizes will be more easily inhaled and a larger fraction of that exposure will reach the pulmonary region, which leads to systemic uptake. Smaller particle sizes also exhibit faster systemic uptake. The model may be used to examine the impact of particle size on lung and systemic body-burdens and clearance. A sample evaluation of 1 and 5 micron particle sizes is presented in Figure 9.

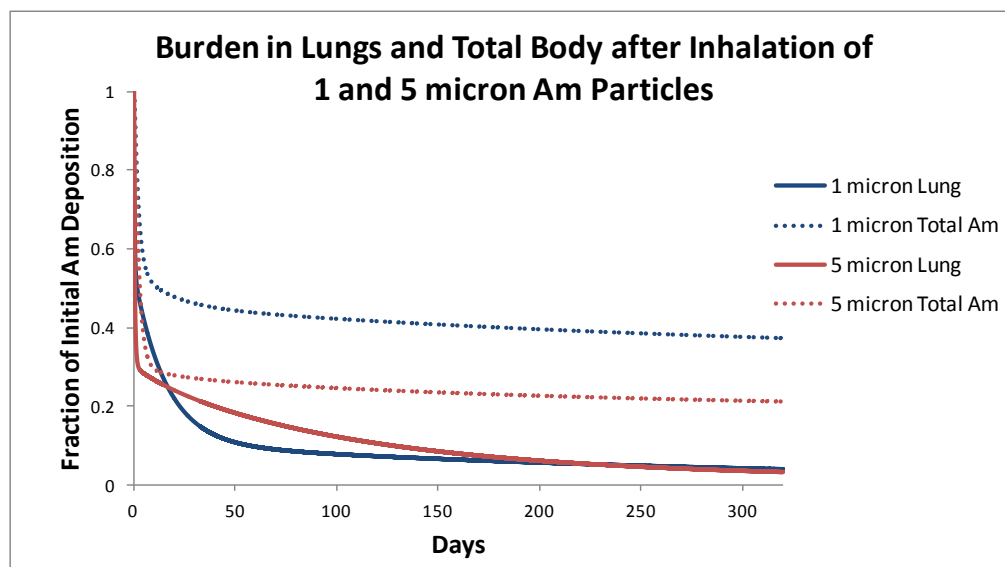


Figure 9. Am Burden in Lung and Total Body as a Function of Particle Size

Since particle size has such a significant impact on the precise deposition and resulting clearance of the Am intake, the particle size distribution will significantly impact radiation dose. While faster clearance with smaller particle sizes may increase the systemic body-burden of Am, larger particle sizes that clear more slowly will result in a higher localized exposure to radiation in the lung. The model also allows one to examine the impact of particle size on target organ doses as well as whole-body effective doses. The impact of particle size (1 and 5 microns) is illustrated in Figure 10.

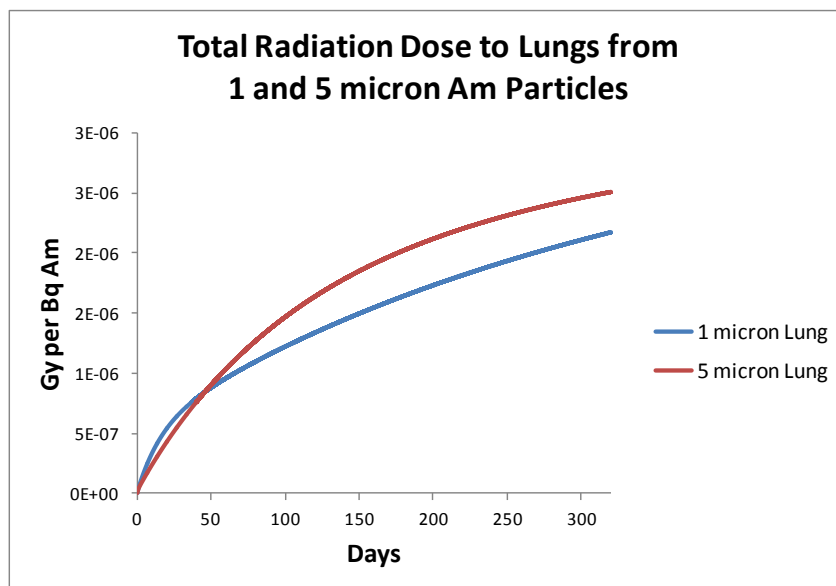


Figure 10. Impact of Radiation Dose to the Lung from Different Particle Sizes

5.2.2. Americium Tissue Distribution

The model allows for an examination of the simple distribution of americium throughout the body. Figure 11 illustrates americium distribution in selected tissues over 30 days in an untreated scenario with an intake of 1 μCi Am-241 (inhalation exposure to AmO_2 , 5 μm particles, 20 L/min breathing rate). Americium has an affinity for the liver and bone compared to other tissues. This illustration also shows how americium has an initial fast clearance from the respiratory tract for a portion of the intake, which then slows dramatically. Americium absorbed from the lungs redistributes and quickly accumulates in the liver and bone.

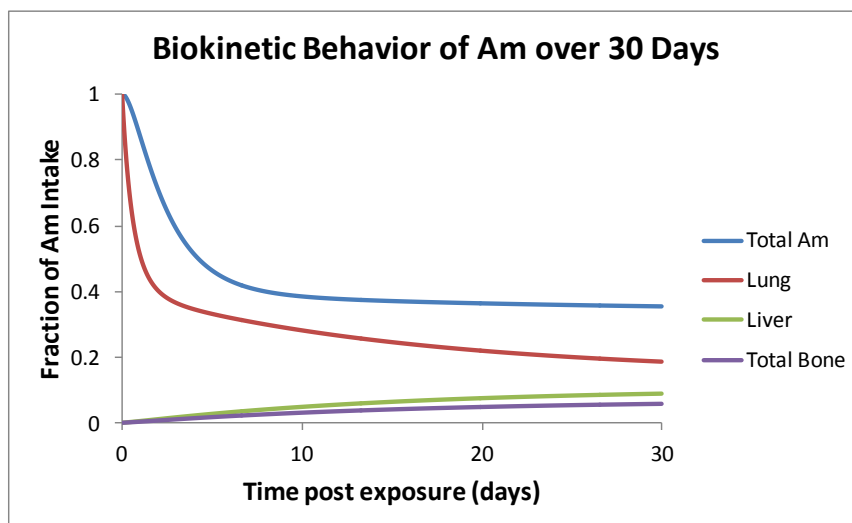


Figure 11. Americium Retention in Selected Tissues Over 30 Days

The total Am in Figure 11 is calculated by summing the Am present in all of the tissues represented in the model for each time step. Additional organ and tissue distributions that could not be easily displayed in Figure 11 are illustrated in Figure 12 and their distribution is extended out to 180 days to show the cross-over in soft tissue distributions. Figure 12 illustrates that the blood has a minimal amount of americium, having been redistributed to tissues, which retain the americium to varying degrees. The different soft tissue compartments represent tissues that have rapid, intermediate, and slow turnover.

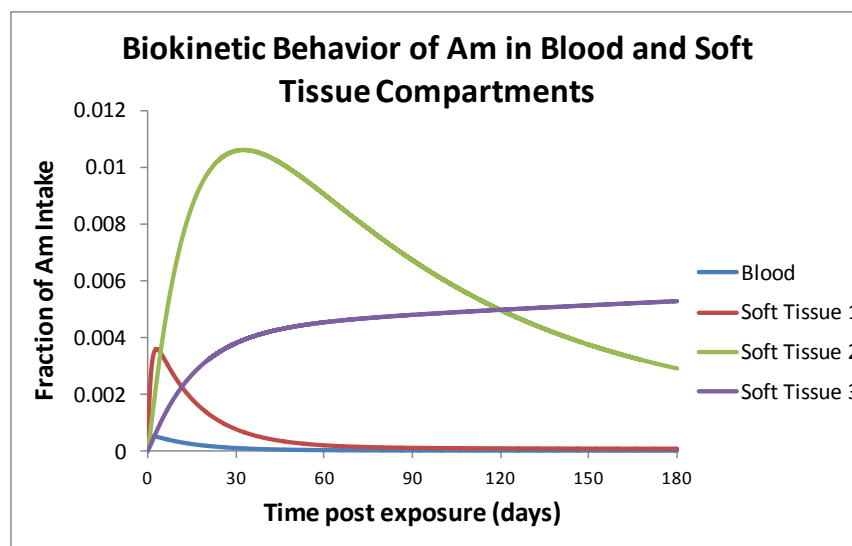


Figure 12. Am Distribution for Selected Tissues Over 90 Days

5.2.3. Comparison of Predicted Americium Retention to Experimental and Human Data

Data collected on humans indicates large variability in americium retention and biokinetics. The precise distribution can be dramatically influenced by the chemical form of americium, the

particle size distribution of the exposure, and breathing rate. Age, gender, and body weight can also impact the outcome.

The biokinetic model for americium developed by Leggett (1992) and implemented in our model has been compared to experimental animal data and human case studies (Leggett 1992). Figure 13 shows the urinary excretion data after an individual was accidentally exposed to AmO₂ as compared to simulation results. In this case, chest measurements indicated a slower respiratory clearance than Leggett's simulation default value of 11 days. The clearance observed in these cases was more consistent with clearance expected from larger particle sizes. Therefore, Leggett used a half-time of 30 days for lung clearance in this simulation.

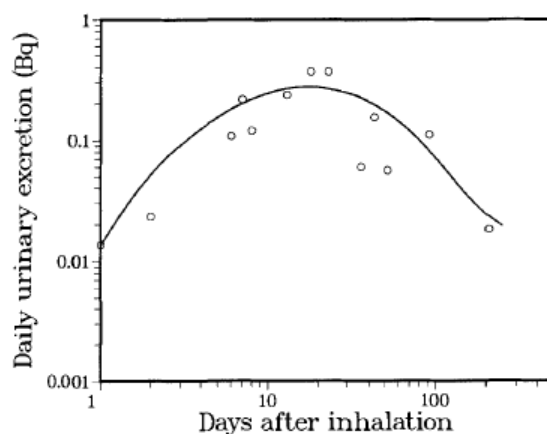


Figure 13. Model Predictions of Am Retention (Leggett 1992)

The americium uptake and biokinetic models were used to compare data from different case studies. The Am uptake and biokinetic models simulate the exposure scenario of a minor Am-241 inhalation following an untreated patient for over six years (Kathren 2003). The case study did not provide details concerning the quality of exposure (chemical form, particle size, or breathing rate). The best fit for the case study results was retroactively applying simulated data (assuming the chemical form to be AmO₂) of a 1 µm particle size exposure with a 15 L/min breathing rate. Observed data on whole-body retention and americium content in bone, liver, and lung are compared to simulation results at 2135 days post exposure in Table 6.

Table 6. Comparison of Case Study Data to Model Predictions

| | Whole-Body (Bq) | Lung (Bq) | Bone (Bq) | Liver (Bq) |
|-------------------|-----------------|-----------|-----------|------------|
| Kathren 2003 | ~205* | 82±6 | 165±14 | 41±4 |
| Model predictions | 198 | 92 | 137 | 37 |

*Quantitative value not provided for this data point. The data point was estimated from the graph provided in the publication.

As described in Section 4.4.5, the model was used to simulate the parameters from the beagle dog study (Guilmette 1989). A 1.2 micron particle exposure with an 15 L/min breathing rate

were used to generate biokinetic data of over 64 days. Americium retention at 64 days post-exposure (reported as percent initial intake) in the whole body and select tissues in untreated animals are compared to simulation results in Table 7.

Table 7. Comparison of Experimental Animal Data to Model Predictions

| | Beagle Study (% Intake) | Model Results (% Intake) |
|------------|-------------------------|--------------------------|
| | <i>Untreated</i> | <i>Untreated</i> |
| Lung | 24.5±2.5 | 19.3 |
| Liver | 25.1±3.4 | 34.3 |
| Bone | 21.8±4.2 | 22.3 |
| Total Body | 76.7±7.8 | 81 |

5.2.4. DTPA Decorporation of Americium

DTPA treatment can reduce the amount of americium in the body by binding the americium in the circulation, as described in section 4.4.4. DTPA predominately binds americium in the systemic circulation and extracellular Am-241 in the interstitial space of tissues. Americium is then re-equilibrated according to the variable transfer rates of the different tissues. The impact of DTPA on americium whole-body retention is illustrated in Figure 14. This figure shows americium retention over 60 days after 1 μ Ci lung deposition in the untreated case and with DTPA treatment beginning at day 10 after exposure, with standard dosing (1 gram daily) for a duration of 30 days (1 μ m particle size, 15 L/min breathing rate).

The red curve shows a rapid decline of americium after treatment is initiated. When treatment is discontinued after 30 days, the slope of the treated curve resumes the shape of the untreated curve and is parallel to it.

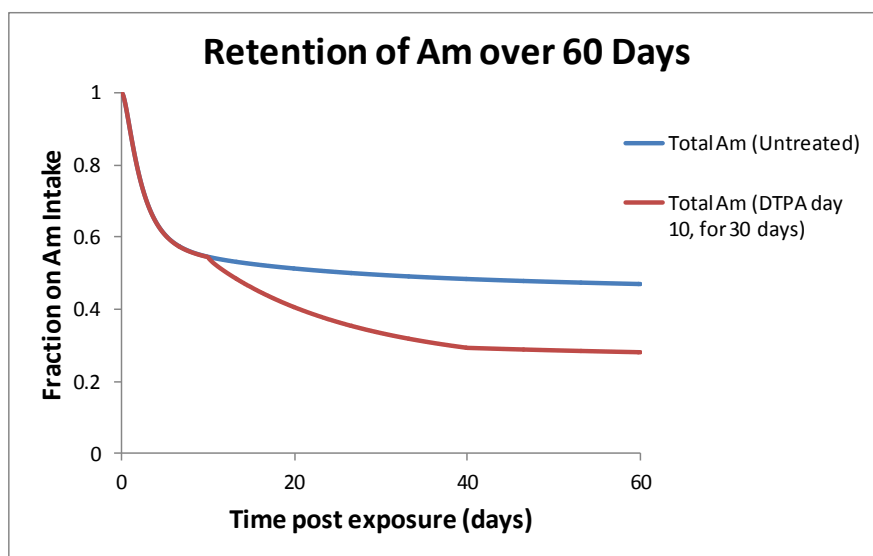


Figure 14. Americium Retention With and Without Treatment

Large individual variability is observed in the retention and clearance of americium with DTPA treatment, comparable to the variability observed with americium biokinetics in individuals. Increased urinary excretion under DTPA treatment ranges from 2-fold to as much as 140-fold, depending on the exposure conditions, in particular the chemical form of americium involved in the initial exposure (Fasiska 1971, Whalen 1972, Cohen 1979, Rosen 1980, Roedler 1989).

5.2.5. Americium Excretion

The composite model estimates cumulative excretion as a function of time. The excretion rate of americium changes over time as it is cleared from the respiratory tract by different modes with different half-times. The cumulative excretion over 60 days from the scenario presented in the previous section (5.2.4) is shown in Figure 15. Total excretion is dominated by fecal excretion early in time, due to the rapid clearance from the ET and TB regions via the GI tract.

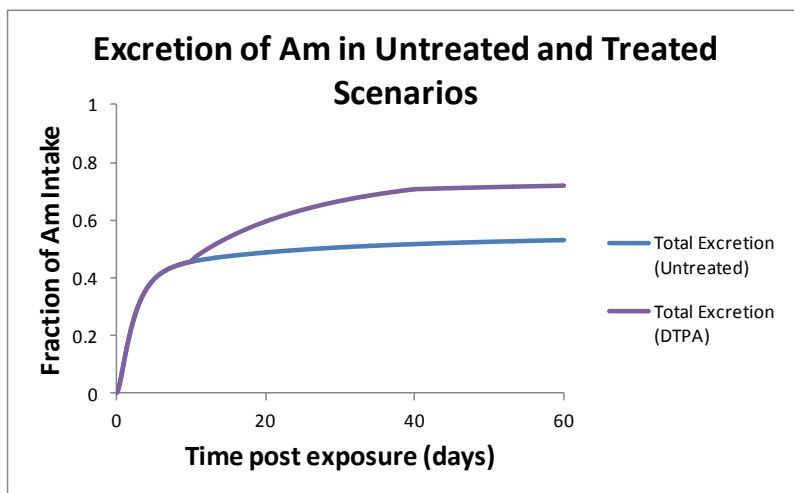


Figure 15. Americium Excretion With and Without Treatment

The impact on urinary excretion during treatment for this scenario is shown in Figure 16. The urinary output quickly declines after treatment ends. The output after stopping treatment is less than pre-treatment values, due to the time required for re-equilibration from slow transfer tissue compartments to the circulation.

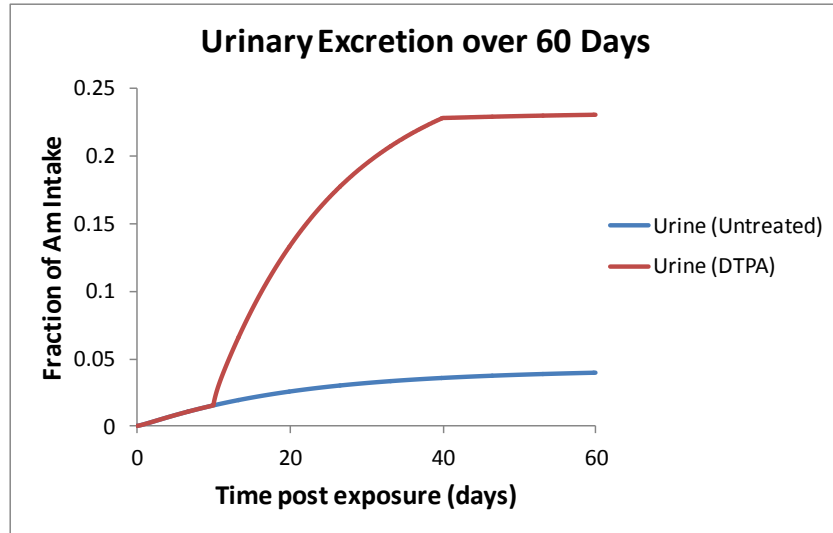


Figure 16. Urinary Excretion of Am With and Without Treatment

The cumulative excretion by different modes starting at day 30 is presented in Figure 17. By day 30, the amount of americium being cleared through the GI tract has diminished, as evidenced by decreased fecal excretion. Urinary excretion is still less modest without DTPA treatment (initiated on day 10, ending on day 40). The figure shows increased urinary output for the treated case, which quickly declines after treatment is stopped. A slightly lower fecal excretion during treatment is due to the decrease in systemic americium cleared via the GI tract during treatment.

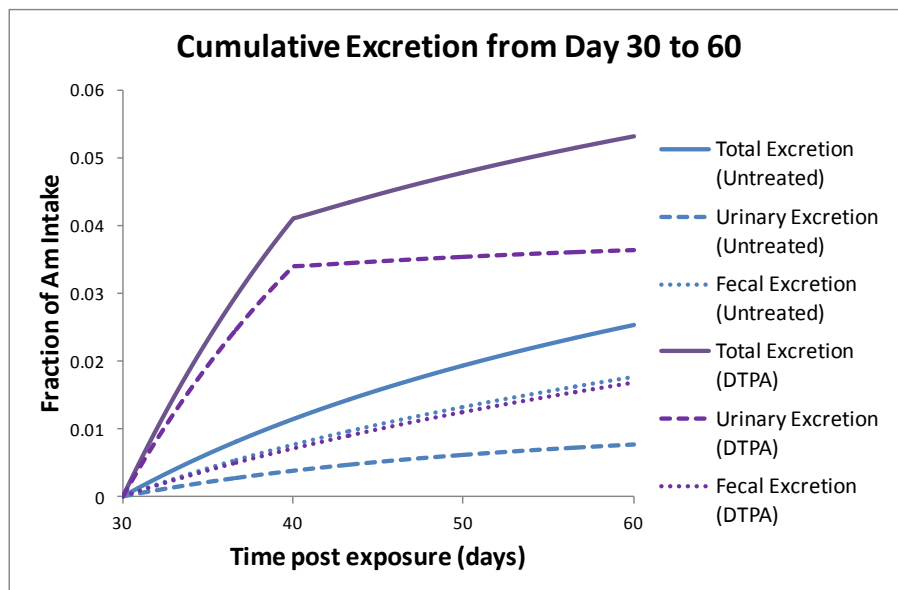


Figure 17. Americium Excretion by Different Modes from Day 30 to 60

5.2.6. Americium Acute and Whole-Body Effective Doses

The model may be used to calculate acute doses to the critical target organs (red bone marrow and lung) and the whole-body effective dose. Since Am-241 has an α -emission, a high radiation dose delivered directly to the lung tissue is possible. The red bone marrow is one of the more sensitive organs for acute effects and americium can be immobilized in bone. Red bone marrow exposure to radionuclides may cause acute effects, such as the hematopoietic radiation syndrome. Our model can determine the dose to these critical organs as a function of time as well as the committed effective whole-body dose.

The acute lung and red marrow doses for a respiratory deposition of 1 μ Ci of Am-241 in an untreated case are shown in Figure 18. The acute dose refers to the total energy deposited in a particular organ and potentially subsequent acute effects (i.e. cell death, which results in organ dysfunction leading to morbidity and mortality). The dose to the lung begins to decline as activity is cleared from the region. The dose to the red marrow accumulates as americium is redistributed from the lung and incorporated into the bone compartments.

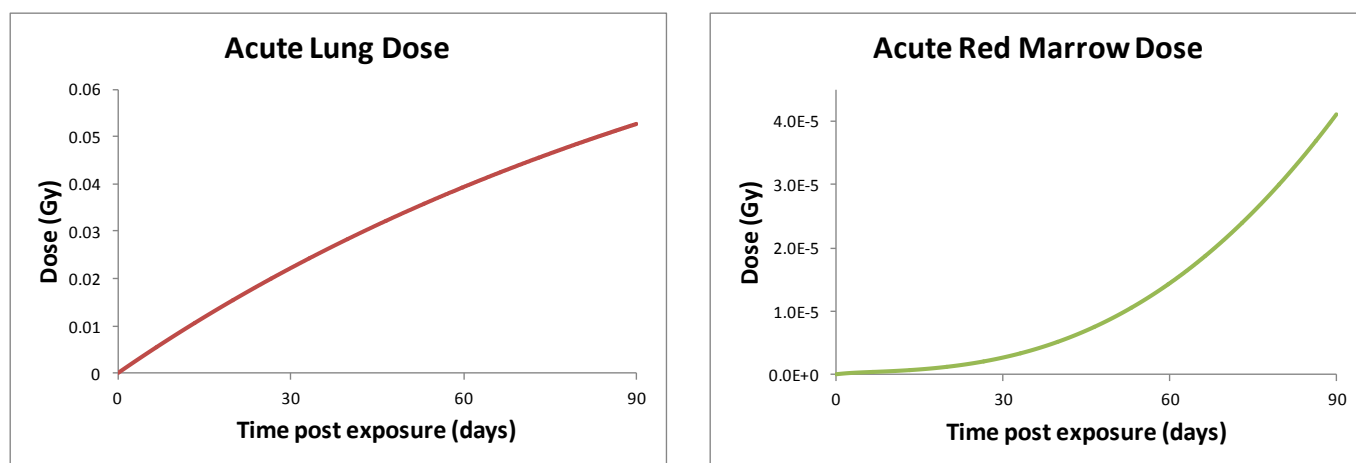


Figure 18. Acute Doses to Critical Organs from Am-241 Over 90 Days

The concept of committed effective dose was developed to relate long-term health effects such as carcinogenesis. For this relationship, tissues must be weighted, since different tissues have different dose responses to carcinogenesis. This weighting results in an averaging of the dose over the whole body, according to tissue-specific sensitivities and the effective whole-body dose is calculated.

The long-term health risk of cancer is most often evaluated calculating the 50-year committed whole-body effective dose. Table 8 shows the predicted 50-year committed whole-body effective dose in treated and untreated scenarios after exposure to 1 μ Ci of Am-241, 5 μ m particulates. The treated scenarios involve a treatment start time of 10 days post-exposure and durations of 30 days, 90 days, and 180 days.

Table 8. 50-Year Radiation Doses from Am-241 in Untreated and Treated Cases

| Dose | Untreated | DTPA Day 10, 30-day Course | DTPA at Day 10, 90-day Course | DTPA at Day 10, 180-day Course |
|--------------------------|------------------|---------------------------------------|--|---|
| Effective Whole-Body, Sv | 1.05 | 0.81 | 0.51 | 0.30 |

The data in Table 8 illustrates reduction in the 50-year committed dose by 23, 51, and 71%, with DTPA treatment beginning day 10 and continuing for 30, 90, or 180 days, respectively. DTPA treatments afford substantial dose reduction from Am-241, allowing substantial reduction in long-term health risks.

The acute dose calculations from our model were compared to the current approach used by the ICRP and adopted by the NCRP (ICRP 1993, NCRP 2008). Our model uses the same biokinetic model as the referenced models; however, the respiratory clearance model differs and is specific to americium with particle size dependence. The ICRP and NCRP approaches use a standard, generic respiratory clearance model developed by ICRP (ICRP 1994). For AmO₂, the ICRP generic model has not reliably predicted clearance from moderately soluble or insoluble parameters; clearance and biokinetics fall somewhere between the two (Kathren 2003). However, the comparison does provide reassurance that the values obtained are of the same magnitude.

Table 9. Comparison of Doses at 365 Days (Gy/Bq of Am-241 Intake) by Different Models

| | Lung - Low LET | Lung - High LET | Red Marrow - Low LET | Red Marrow - High LET |
|------------------|---------------------------|----------------------------|---------------------------------|----------------------------------|
| NCRP 2008 | 3.9x10 ⁻⁹ | 1.1x10 ⁻⁶ | 6.6x10 ⁻¹⁰ | 8.1x10 ⁻⁸ |
| Model simulation | 1.4x10 ⁻⁹ | 3.2x10 ⁻⁶ | 2.6x10 ⁻¹⁰ | 3.3x10 ⁻⁸ |

5.2.7. Evaluation of Efficacy

The efficacy of DTPA treatment can be evaluated based on the concept of dose reduction. The example above, in Table 8, is a good illustration of how the comparison of doses after DTPA treatment can be used to evaluate efficacy. This type of analysis can also allow an end-user to determine how long DTPA treatment administration is justified. The dose reduction from treatment is further illustrated in Figure 19, which shows the dose accumulated over 90 days in untreated and treated cases from a 1 µCi intake of Am-241 (inhalation exposure to AmO₂, 5 µm particles, 20 L/min breathing rate). The treated cases assume treatment starting one day after the exposure and continuing for 30 or 90 days. A significant reduction in dose is observed with treatment for 30 days and dose is further reduced with longer treatment times.

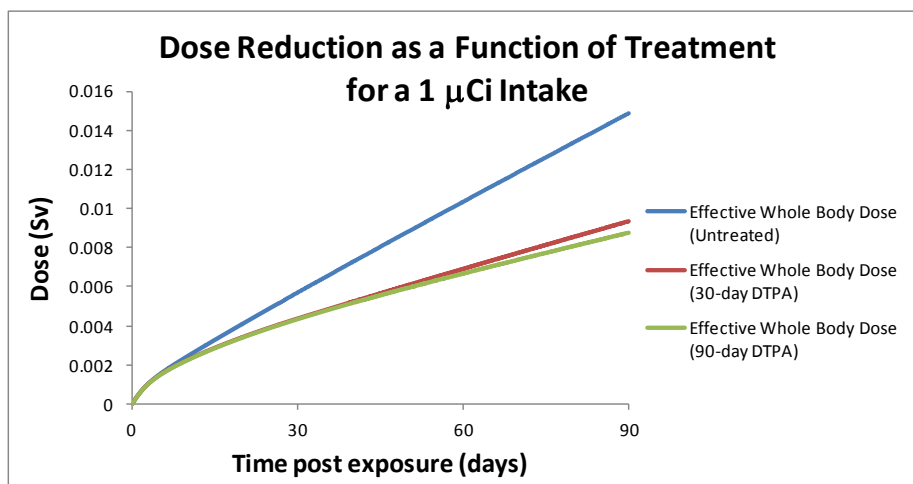


Figure 19. Doses from Am-241 Over 90 Days in Treated and Untreated Cases

The dose saving reduces with time, which illustrates that the majority of the dose absorbed by the body is received very early after an exposure. The time of treatment with DTPA can have a significant impact on the overall dose resulting from Am exposure. This is particularly important for actinides such as americium and plutonium because of their incorporation into bone. After americium is absorbed into the systemic circulation from the lungs, a portion can quickly be retained in the bone where DTPA has minimal ability to remove it. Having DTPA present in the circulation can help bind americium as soon as it is absorbed from the lung and reduces the amount available for incorporation into the bone. It is worth noting, that extended treatment times are often necessary due to the slow clearance fractions of americium from the lungs. Unfortunately, DTPA injections have not consistently shown to effectively increase the absorption of Am from the lungs. Therefore, a significant portion of the dose observed in Figure 19 arises from the americium lodged in the respiratory tract.

A correlation between the lag-time for the initiation of treatment and the efficacy of treatment is examined. In the example shown in Table 10, the 90-day dose from 1 μCi of Am-241 is reduced more dramatically the sooner treatment initiation occurs. Efficacy of treatment reduces with an increase in time before treatment initiation. However, because DTPA has little or no influence on absorption of Am from the lungs, no significant dose reduction is afforded to that tissue compartment.

Table 10. Doses after 90 Days from 1 μ Ci Am-241 Exposure in Untreated and 30-Day DTPA Treated Subjects with Different Treatment Initiation Times

| Dose | Untreated | DTPA at day 14, 30-day course | DTPA at day 7, 30-day course | DTPA at day 3, 30-day course | DTPA at day 1, 30-day course |
|---------------------------|------------------|--------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Lung, mGy | 50 | 50 | 50 | 50 | 50 |
| Red Marrow, mGy | 0.1 | 0.07 | 0.05 | 0.03 | 0.01 |
| Effective Whole-Body, mSv | 15 | 13 | 11 | 10 | 9 |

Dose reduction is further examined in Table 11 where the 50-year effective whole-body dose versus treatment initiation time and duration of treatment are presented.

Table 11. 50-Year Committed Whole-Body Effective Doses (Sv)

| Duration of DTPA, days | <u>Treatment Initiation Times (days post exposure)</u> | | | | | | |
|-------------------------------|---|-----------|-----------|-----------|------------|------------|------------|
| | 0 | 30 | 60 | 90 | 120 | 150 | 180 |
| 0 | 1.74 | - | - | - | - | - | - |
| 30 | 0.94 | 1.56 | 1.65 | 1.67 | 1.68 | 1.68 | 1.69 |
| 60 | 0.82 | 1.49 | 1.60 | 1.62 | 1.63 | 1.64 | 1.64 |
| 90 | 0.80 | 1.45 | 1.55 | 1.58 | 1.59 | 1.59 | 1.60 |
| 120 | 0.80 | 1.41 | 1.51 | 1.54 | 1.55 | 1.56 | 1.56 |
| 150 | 0.80 | 1.38 | 1.48 | 1.50 | 1.51 | 1.52 | 1.53 |
| 180 | 0.80 | 1.35 | 1.45 | 1.47 | 1.48 | 1.49 | 1.50 |

The data illustrate that earlier treatment initiation enables greater reduction of dose. Likewise, longer courses of DTPA generally provide greater dose reduction. However, at later treatment initiation times, dose reduction is not as significant even with longer treatment durations. The dose reduction factors for these same data may be calculated by dividing the treated dose by the untreated dose.

$$Dose\ reduction\ factor = Dose_{Treated}/Dose_{Untreated}$$

The dose reduction factors for the different treatment courses, summarized in Table 11, are listed in Table 12.

Table 12. Dose Reduction Factors for Different Treatment Regimens

| Duration of DTPA, days | <u>Treatment Initiation Times (days post exposure)</u> | | | | | | |
|------------------------|--|------|------|------|------|------|------|
| | 0 | 30 | 60 | 90 | 120 | 150 | 180 |
| 30 | 0.54 | 0.90 | 0.95 | 0.96 | 0.97 | 0.97 | 0.97 |
| 60 | 0.47 | 0.86 | 0.92 | 0.93 | 0.94 | 0.94 | 0.94 |
| 90 | 0.46 | 0.83 | 0.89 | 0.91 | 0.91 | 0.91 | 0.92 |
| 120 | 0.46 | 0.81 | 0.87 | 0.89 | 0.89 | 0.90 | 0.90 |
| 150 | 0.46 | 0.79 | 0.85 | 0.86 | 0.87 | 0.87 | 0.88 |
| 180 | 0.46 | 0.78 | 0.83 | 0.84 | 0.85 | 0.86 | 0.86 |

The values in Table 12 may be converted to estimates of efficacy by subtracting the dose reduction factors from one.

$$Efficacy = 1 - \text{Dose reduction factor}$$

The efficacy values are shown in Table 13. The higher values indicate more effective treatment and greater efficacy. Earlier treatment combined with longer duration affords the greatest dose reduction and efficacy.

Table 13. Efficacy of Different Treatment Regimens

| Duration of DTPA, days | <u>Treatment Initiation Times (days post exposure)</u> | | | | | | |
|------------------------|--|------|------|------|------|------|------|
| | 0 | 30 | 60 | 90 | 120 | 150 | 180 |
| 30 | 0.46 | 0.10 | 0.05 | 0.04 | 0.03 | 0.03 | 0.03 |
| 60 | 0.53 | 0.14 | 0.08 | 0.07 | 0.06 | 0.06 | 0.06 |
| 90 | 0.54 | 0.17 | 0.11 | 0.09 | 0.09 | 0.09 | 0.08 |
| 120 | 0.54 | 0.19 | 0.13 | 0.11 | 0.11 | 0.10 | 0.10 |
| 150 | 0.54 | 0.21 | 0.15 | 0.14 | 0.13 | 0.13 | 0.12 |
| 180 | 0.54 | 0.22 | 0.17 | 0.16 | 0.15 | 0.14 | 0.14 |

5.2.8. Practical Application of Model Results

Results from the model help in evaluating potential effects resulting from various exposure scenarios. For example, acute effects can be projected from the estimated dose to critical target organs. High levels of exposure are required to reach doses that will induce acute effects in the lung such as radiation pneumonitis and fibrosis. The I_{50} (symptomatic incidence in 50% of the population) for pneumonitis is approximately 10 Gy, although the data from clinical radiology are highly variable and greatly dependent on the dose rate (Marks 2010). The LD_{50} for the red

bone marrow is 2.9 Gy (Anno 2003) for acute exposures; accumulating the dose over a longer period of time will increase this value. For very high dose scenarios, the model can be used to look at how aggressive and/or effective treatment can be.

At lower doses, protection from long-term health effects, such as carcinogenesis, is the primary concern of internalized radionuclides. Each branch of the U.S. Department of Defense sets guidance and recommended dose limits. As an example, the U.S. Navy limits the 50-year whole-body committed effective dose to 0.05 Sv or 0.5 Sv for any specific organ or tissue, whichever is more limiting (NAVMED P-5055). The model can help to resolve the treatment duration required, to lower the committed dose within these limits. The recommended threshold for decorporation treatment is any exposure resulting in a 50-year whole-body committed effective dose greater than 200 mSv (Rojas-Palma 2009). Therefore, the model can also help to determine whether treatment is necessary.

Section 6.

Limitations of the Model

The composite model described in this report is based on the best, currently available data; however, as will all models, it has a number of limitations. Large variability in intake, clearance, and biokinetics after americium exposures has been observed among individuals as well as in animal experiments. Furthermore, intake, clearance, and biokinetics vary significantly, depending on the specific particle size, breathing rate, and chemical form of the exposure. The model can only provide a tool for evaluating specific scenarios and testing different treatment regimens with fixed assumptions. For actual exposure, observed bioassay data for each individual must be used to determine the actual clearance, biokinetics, and resulting dose for that person.

The biokinetic model is currently limited by the data available on tissue distribution of americium. It assumes three generic soft tissue compartments, which clear at varying rates. If actual data on the other organs were available, more precise dose estimates would be possible. More detailed data on specific organ burdens may become available in the future as autopsy samples from the United States Transuranium and Uranium Registries (USTUR) are analyzed. Based on animal data, it is known that a fraction of the less soluble americium in the pulmonary region is transferred to the lymph nodes and eventually to the blood stream with a long half-life. In our model, the lymph nodes are not treated as a separate compartment due to a lack of human data and the minor contribution of this transfer mode.

Finally, our model's removal of americium with DTPA is an approximation, based on the physiological distribution of DTPA and americium, the observed data, assumptions concerning the DTPA binding, and interstitial availability of americium. The approximation affords reasonable results; however, no quantitative data is available on the interstitial availability of americium. Another approach to model decorporation with DTPA has been conducted with plutonium (Pu) based on molecular chelation kinetics (Breustedt 2009, 2010). In this approach, the molecular ratios of plutonium, DTPA, and their binding affinities were used to calculate Pu-DTPA formation and subsequent excretion. The investigators reported that approach did not provide suitable results when modeling repeatable DTPA administration over a short time period. Also, the challenge with modeling molecular chelation kinetics when the components (Pu and DTPA) are present on vastly different scales was also discussed. This approach may still afford a plausible model, provided further development and experimental data is available and could apply to americium.

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Section 7.

Next Steps

Each of the components of the Am decorporation model will be consolidated into a single set of codes and integrated into user-friendly software for use in scenario simulations. These components include the inhalation exposure model, the americium biokinetic model, the DTPA treatment model, and the radiation dose models. The results presented here provide an indication of the utility of the composite model and a sample of the type of data that can be generated.

As mentioned previously, large individual variability was observed in human data collected, to date, regarding americium absorption, retention, and response to treatment. Although, beyond the scope of the current effort, certain aspects of individual variability could be addressed in the americium decorporation model presented here. For example, the distribution of americium is known to be dependent on age, gender, and body size/composition. Distribution is partially due to the differences in the relative size of the tissues and partially due to differences in metabolism. Physiological data exists for age and gender specific variances. Extrapolations can be made mathematically for some parameters, to account for body size and composition. Therefore, the physiological model for americium, as well as the DTPA treatment model could be refined to account for physiological differences in distribution and retention of americium, so that additional age and gender specific data could be generated. Likewise, the absorption of radiation is impacted by the differential tissue distribution of radioactivity. Furthermore, long-term health risks vary among different ages and between genders. Model refinements would also enable more precise health risk assessments outside of the “healthy, adult male”.

As mentioned in the previous section, modeling decorporation of americium on the level of molecular chelation might afford a more precise description of the rate of removal americium under DTPA treatment. However, this level of modeling would require more detailed data on americium and DTPA distribution and kinetics in tissues than is currently available. The effort would also involve more complex modeling. However, with additional data and resources, this may prove a viable approach to resolving some of the uncertainty in the current model.

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Section 8.

Conclusions

The DTPA decorporation model presented in this work estimates americium absorption, distribution, retention, excretion, and response to DTPA treatment in adult healthy males after an inhalation (or ingestion) exposure. The model further estimates the acute lung and red bone marrow dose and the whole-body effective dose as a function of time.

The results of the model compare favorably with both human data and alternative models developed by the ICRP and NCRP.

Calculations from the model may be used to analyze consequences of exposure to Am-241 and the effect of treatment based on initiation and duration times. The model may facilitate interpretation of Am bioassay data and aid in treatment planning. The Am decorporation model is a valuable tool for assessing the effect of exposure to Am-241 and DTPA treatment.

The model could be further improved by incorporating age and gender specific parameters and data, which would enable more precise calculations for additional segments of the population.

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Section 9.

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Section 10.

Definitions, Acronyms, and Abbreviations

| | |
|----------|--|
| AMedP-8 | Allied Medical Publication 8 |
| ARA | Applied Research Associates, Inc. |
| DoD | Department of Defense |
| DTPA | Diethylenetriaminepentaacetate (or diethylenetriaminepentaacetic acid) |
| DTRA | Defense Threat Reduction Agency |
| FDA | Food and Drug Administration |
| GI | Gastrointestinal tract |
| Gryphon | Gryphon Scientific, LLC |
| ICRP | International Commission on Radiological Protection |
| JPEO-CBD | Joint Program Executive Office for Chemical/Biological Defense |
| JPM-IS | Joint Program Manager Information Systems |
| JSTO | Joint Science and Technology Office |
| MCM | Medical Countermeasure Model |
| MPPD | Multiple-Path Particle Dosimetry |
| NCRP | National Council on Radiation Protection and Measurements |
| NRC | National Research Council |
| PBPK/PD | Physiologically Based Pharmacokinetic/Pharmacodynamic |
| SAF | Specific absorbed fraction |

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Appendix A.

Inhalation Exposure Model

As described in Figure 3, the inhalation exposure model will determine the amount of americium deposited in the three major regions of the respiratory tract, based on Am air concentration, duration of exposure, wind speed, breathing rate, and particle size distribution. Example outputs from the model for different particle sizes and breathing rates are provided in Table 14 and Table 15. In Table 14, the fraction of the exposure that actually gets deposited in the respiratory tract and determines the intake is provided for two different particle sizes and breathing rates. In these cases, intake is defined as the amount of material deposited in the respiratory tract. The estimates show that the intake is significantly impacted by the particle size of the exposure and, to a lesser degree, the breathing rate.

Table 14. Fraction of Exposure Deposited in the Three Primary Respiratory Regions

| Region | Particle Size and Breathing Rate | | | |
|------------------|----------------------------------|-----------------------------|-----------------------------|-----------------------------|
| | 1 μm 15 L/min | 1 μm 20 L/min | 5 μm 15 L/min | 5 μm 20 L/min |
| Extra-thoracic | 0.006 | 0.007 | 0.208 | 0.240 |
| Tracheobronchial | 0.061 | 0.066 | 0.266 | 0.294 |
| Pulmonary | 0.093 | 0.086 | 0.260 | 0.226 |

Since the three regions clear at different rates and by different modes (see section 4.2.6), particle size and breathing rate further impact the fate of americium in the body and ultimately the dose received. Larger particle sizes and faster breathing rates yield overall greater total intake (see Table 14).

In many case studies, the intake is determined after an event by external chest measurements of the soft photon from Am-241. Calculating intake provides the fraction of the intake for each region (Table 15), used to estimate the amount of the intake in each of the three respiratory regions.

Table 15. Fraction of Intake Deposited in the Three Primary Respiratory Regions

| Region | Particle Size and Breathing Rate | | | |
|------------------|----------------------------------|-----------------------------|-----------------------------|-----------------------------|
| | 1 μm 15 L/min | 1 μm 20 L/min | 5 μm 15 L/min | 5 μm 20 L/min |
| Extra-thoracic | 0.04 | 0.04 | 0.28 | 0.31 |
| Tracheobronchial | 0.38 | 0.42 | 0.36 | 0.39 |
| Pulmonary | 0.58 | 0.54 | 0.36 | 0.30 |

For use in the uptake portion of the model, these fractions are calculated by adding the total amount of Am deposited in the respiratory tract, Am_d , which is:

$$Am_d = ET_d + TB_d + P_d$$

where ET_d , TB_d , and P_d are the amounts of Am deposited in the respective regions. The fractions of the total Am deposited in the ET, TB, and P regions are:

$$ET_f = ET_d / Am_d$$

$$TB_f = TB_d / Am_d$$

$$P_f = P_d / Am_d$$

where ET_f , TB_f , and P_f are the fractions of Am deposited in the respective regions. The fractions are then implemented in the respiratory clearance and uptake model described in Appendix B.

Appendix B.

Respiratory Clearance and Uptake Model

The respiratory clearance model uses the initial amount of americium in the ET, TB, and P (ET_o , TB_o , and P_o) regions to calculate the amount and rate of transfer from the respiratory tract to either the GI tract via ingestion or directly to the blood stream via absorption. According to the parameters listed in Table 1, the amount of americium in the pulmonary region behaving according to the fast ($P1_o$), moderate ($P2_o$), and slow ($P3_o$) fractions is provided by:

$$P1_o = P_o * 0.8$$

$$P2_o = P_o * 0.17$$

$$P3_o = P_o * 0.03$$

The amount of Am in each of the regions over time is:

$$ET_t = ET_o * 1 * (0.5^{\lambda_1 t})$$

$$TB_t = TB_o * 1 * (0.5^{\lambda_2 t})$$

$$P1_t = P1_o * 0.9 * (0.5^{\lambda_3 t})$$

$$P1_t = P1_o * 0.1 * (0.5^{\lambda_4 t})$$

$$P2_t = P2_o * 1 * (0.5^{\lambda_5 t})$$

$$P3_t = P3_o * 0.2 * (0.5^{\lambda_6 t})$$

$$P3_t = P3_o * 0.8 * (0.5^{\lambda_7 t})$$

where the initial concentration in each region is multiplied by the fraction in each region going to either the GI tract or blood and t is time post-exposure in days. The transfer rates of Am are determined by the rate constants (inverse of the half-times in days, values shown in Table 2).

λ_1 is the rate constant for transfer from the ET region to the GI tract

λ_2 is the rate constant for transfer from the TB region to the GI tract

λ_3 is the rate constant for transfer from the P1 region to the blood**

λ_4 is the rate constant for transfer from the P1 region to the GI tract

λ_5 is the rate constant for transfer from the P2 region to the GI tract

λ_6 is the rate constant for transfer from the P3 region to the blood

λ_7 is the rate constant for transfer from the P3 region to the GI tract

**This rate constant is particle size-dependent as described in Section 4.2.5.

The amount of Am transferred from the respective regions to the blood or GI tract at time t is then calculated:

$$Am_{ET \rightarrow GI} = -\ln 2 * \lambda_1 * ET_t$$

$$Am_{TB \rightarrow GI} = -\ln 2 * \lambda_2 * TB_t$$

$$Am_{P1 \rightarrow Blood} = -\ln 2 * \lambda_3 * P1_t$$

$$Am_{P1 \rightarrow GI} = -\ln 2 * \lambda_4 * P1_t$$

$$Am_{P2 \rightarrow GI} = -\ln 2 * \lambda_5 * P2_t$$

$$Am_{P3 \rightarrow Blood} = -\ln 2 * \lambda_6 * P3_t$$

$$Am_{P3 \rightarrow GI} = -\ln 2 * \lambda_7 * P3_t$$

The amount of americium in the respiratory tract as a function of time t is:

$$\frac{d}{dt}(Am_{respiratory\ tract}) = Am_{ET \rightarrow GI} + Am_{TB \rightarrow GI} + Am_{P1 \rightarrow Blood} + Am_{P1 \rightarrow GI} + Am_{P2 \rightarrow GI} + Am_{P3 \rightarrow Blood} + Am_{P3 \rightarrow GI}$$

The sum of the negative values diminishes the initial value of the total americium in the respiratory tract over time. As the Am contents in the respiratory regions are reduced over time, the values are added to the blood or GI compartments, as appropriate.

Appendix C.

Americium Biokinetic Model

The americium biokinetic model obtains the input from the uptake model to determine the amount of Am in the blood, entering the systemic circulation. The computation is accomplished by solving a series of interdependent differential equations, over a specified period of time:

$$\begin{aligned} \frac{d}{dt}(Am_{blood}) = & -Am_{blood} * TC_{blood \rightarrow liver} + Am_{liver} * TC_{liver \rightarrow blood} - Am_{blood} * TC_{blood \rightarrow ST1} + Am_{ST1} \\ & * TC_{ST1 \rightarrow blood} - Am_{blood} * TC_{blood \rightarrow ST2} + Am_{ST2} * TC_{ST2 \rightarrow blood} - Am_{blood} * TC_{blood \rightarrow ST3} \\ & + Am_{ST3} * TC_{ST3 \rightarrow blood} - Am_{blood} * TC_{blood \rightarrow CS} + Am_{CM} * TC_{CM \rightarrow blood} - Am_{blood} * TC_{blood \rightarrow TS} \\ & + Am_{RM} * TC_{RM \rightarrow blood} - Am_{blood} * TC_{blood \rightarrow K1} - Am_{blood} * TC_{blood \rightarrow ULIC} - Am_{blood} \\ & * TC_{blood \rightarrow K2} + Am_{K2} * TC_{K2 \rightarrow blood} - Am_{blood} * TC_{blood \rightarrow testes} + Am_{testes} * TC_{testes \rightarrow blood} \\ & - Am_{blood} * TC_{blood \rightarrow UBC} \\ & - ((Am_{ET \rightarrow GI} + Am_{TB \rightarrow GI} + Am_{P1 \rightarrow GI} + Am_{P2 \rightarrow GI} + Am_{P3 \rightarrow GI}) * 0.0002) \\ & - (Am_{P1 \rightarrow Blood} + Am_{P3 \rightarrow Blood}) \end{aligned}$$

$$\frac{d}{dt}(Am_{liver}) = Am_{blood} * TC_{blood \rightarrow liver} - Am_{liver} * TC_{liver \rightarrow blood} - Am_{liver} * TC_{liver \rightarrow SIC}$$

$$\frac{d}{dt}(Am_{ST1}) = Am_{blood} * TC_{blood \rightarrow ST1} - Am_{ST1} * TC_{ST1 \rightarrow blood}$$

$$\frac{d}{dt}(Am_{ST2}) = Am_{blood} * TC_{blood \rightarrow ST2} - Am_{ST2} * TC_{ST2 \rightarrow blood}$$

$$\frac{d}{dt}(Am_{ST3}) = Am_{blood} * TC_{blood \rightarrow ST3} - Am_{ST3} * TC_{ST3 \rightarrow blood}$$

$$\frac{d}{dt}(Am_{CM}) = Am_{CS} * TC_{CS \rightarrow CM} + Am_{CV} * TC_{CV \rightarrow CM} - Am_{CM} * TC_{CM \rightarrow blood}$$

$$\frac{d}{dt}(Am_{CS}) = Am_{blood} * TC_{blood \rightarrow CS} - Am_{CS} * TC_{CS \rightarrow CM} - Am_{CS} * TC_{CM \rightarrow CV}$$

$$\frac{d}{dt}(Am_{CV}) = Am_{CS} * TC_{CS \rightarrow CV} - Am_{CV} * TC_{CV \rightarrow CM}$$

$$\frac{d}{dt}(Am_{RM}) = Am_{TV} * TC_{TV \rightarrow RM} + Am_{TS} * TC_{TS \rightarrow RM} - Am_{RM} * TC_{RM \rightarrow blood}$$

$$\frac{d}{dt}(Am_{TS}) = Am_{blood} * TC_{blood \rightarrow TS} - Am_{TS} * TC_{TS \rightarrow RM} - Am_{TS} * TC_{TS \rightarrow TV}$$

$$\frac{d}{dt}(Am_{TV}) = Am_{TS} * TC_{TS \rightarrow TV} - Am_{TV} * TC_{TV \rightarrow RM}$$

$$\frac{d}{dt}(Am_{K1}) = Am_{blood} * TC_{blood \rightarrow K1} - Am_{K1} * TC_{K1 \rightarrow UBC}$$

$$\frac{d}{dt}(Am_{K2}) = Am_{blood} * TC_{blood \rightarrow K2} - Am_{K2} * TC_{K2 \rightarrow blood}$$

$$\frac{d}{dt}(Am_{testes}) = Am_{blood} * TC_{blood \rightarrow testes} - Am_{testes} * TC_{testes \rightarrow blood}$$

$$\frac{d}{dt}(Am_{UBC}) = Am_{K1} * TC_{K1 \rightarrow UBC} + Am_{blood} * TC_{blood \rightarrow UBC} - Am_{UBC} * TC_{UBC \rightarrow urine}$$

$$\frac{d}{dt}(Am_{urine}) = Am_{UBC} * TC_{UBC \rightarrow urine}$$

$$\begin{aligned} \frac{d}{dt}(Am_{GIcontents}) &= Am_{liver} * TC_{liver \rightarrow SIC} + Am_{blood} * TC_{blood \rightarrow ULIC} - Am_{GIcontents} * TC_{GIcontents \rightarrow feces} \\ &\quad - ((Am_{ET \rightarrow GI} + Am_{TB \rightarrow GI} + Am_{P1 \rightarrow GI} + Am_{P2 \rightarrow GI} + Am_{P3 \rightarrow GI}) * 0.9998) \\ \frac{d}{dt}(Am_{feces}) &= Am_{GIcontents} * TC_{GIcontents \rightarrow feces} \end{aligned}$$

where:

TC is transfer coefficient; ST1, 2, and 3 are soft tissues 1, 2, and 3; CS is cortical surface, CM is cortical marrow, CV is cortical volume, TS is trabecular surface, TV is trabecular volume, RM is red bone marrow, and K1 and 2 are kidney compartments 1 and 2. UBC is urinary bladder contents, ULIC is upper large intestine contents, and SIC is small intestines contents. Respiratory parameters are defined in Appendix A and B. Values for transfer coefficients are listed in Table 2.